Molecular Pain

Review

Hot receptors in the brain

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Abstract

Two major approaches have been employed for the development of novel drugs to treat chronic pain. The most traditional approach identifies molecules involved in pain as potential therapeutic targets and has focused mainly on the periphery and spinal cord. A more recent approach identifies molecules that are involved in long-term plasticity. Drugs developed through the latter approach are predicted to treat chronic, but not physiological or acute, pain. The TRPV1 (transient receptor potential vanilloid-1) receptor is involved in nociceptive processing, and is a candidate therapeutic target for pain. While most research on TRPV1 receptors has been conducted at the level of the spinal cord and peripheral structures, considerably less research has focused on supraspinal structures. This short paper summarizes progress made on TRPV1 receptors, and reviews research on the expression and function of TRPV1 receptors in supraspinal structures. We suggest that the TRPV1 receptor may be involved in pain processing in higher brain structures, such as the anterior cingulate cortex. In addition, some regions of the brain utilize the TRPV1 receptor for functions apparently unrelated to pain.

Background

The TRPV1 (transient receptor potential vanilloid-1) receptor was originally isolated using a calcium imaging-based expression method [1-3]. This receptor is activated by capsaicin (the pungent ingredient of hot peppers), protons, and heat (>43°C), and behaves as a non-selective cationic channel with high permeability for calcium [2-6]. A number of endogenous ligands suggested for these receptors include: protons, ATP, lipoxygenase products, anandamide, N-oleoyldopamine, and N-arachidonoyl dopamine [5-7].

TRPV1 receptor subunits are predicted to have six transmembrane spanning domains with an intramembrane loop connecting the 5th and 6th domains [3]. A variety of molecules and proteins interact with and/or modulate the TRPV1 receptor. These include: TRPV3 and phosphitidyli-nositol-4,5-bisphosphate receptor modulation of capsaicin binding [8,9] and interactions with scaffolding and synaptic vesicle proteins [10,11].

The role of the TRPV1 receptor in pain-related behaviors has been demonstrated with gene knockout mice [12]. Specifically, these mice showed impairments in their ability to detect painful heat stimuli, and demonstrated little thermal hypersensitivity during an inflammation test [12]. Responses to noxious mechanical stimulation were not altered by the gene knockout, suggesting a selective modality for the TRPV1 receptor [12]. While this study demonstrates that TRPV1 of the dorsal root ganglia (DRG) neurons modulate nociceptive behaviors, the role of the

TRPV1 in supraspinal brain structures was not investigated.

Most research on the TRPV1 receptor has been conducted on spinal cord and peripheral structures [6,13]. In this review, we highlight studies that report the expression and function of the TRPV1 receptor in supraspinal structures, with particular emphasis on brain regions involved in the processing of pain.

Expression in the brain

A variety of studies have been conducted to determine the expression profile of the TRPV1 receptor throughout the brain [3,14-21] (See additional file 1: Table 1). Initial studies with [3H] resiniferatoxin (RTX), which label TRPV1 receptors, have shown that TRPV1 is expressed in the trigeminal ganglia and DRG [15]. However, no TRPV1 receptor expression was detected in the brain. Confirmation of these findings was obtained with northern blot analysis [3]. Collectively, these results suggest that the TRPV1 receptor is not expressed in the brain.

Acs et al. [17] established that TRPV1 receptors could be detected in the preoptic hypothalamus, locus coeruleus, and ventral thalamus of human and rat brain, using a modified RTX-labeling technique. The existence of TRPV1 receptors in the brain has been supported numerous times with assays for both TRPV1 protein and mRNA [14,16,18-22] (for example, Fig. 1). One of the most comprehensive studies was conducted by Roberts et al. [18] in which RTX labeling in the brain of TRPV1 knockout mice was compared to mice with the TRPV1 gene. This study revealed a wide distribution of TRPV1 receptors in the brain, including regions of the cerebral cortex, cerebellum and a variety of subcortical structures. It should be emphasized that TRPV1 RNA is approximately 28 times greater in the DRG than in any other brain region [21]. Thus, the most likely explanation for the absence of TRPV1 detection in the brain, described by other investigators [3,15], is that their assays were not sensitive enough to detect the lower expression in the brain.

The TRPV1 receptor is localized to neuron cell bodies and dendrites, astrocytes, and perivascular structures within the brain [14,16,18,19]. TRPV1 can be detected predominantly on postsynaptic spines at the subcellular level [19]. In addition, TRPV1 can be detected in pericytes and at the feet of astrocytes surrounding small vessels [19]. It has also been demonstrated that TRPV1 co-localizes and physically interacts with TRPV2 receptors within the brain [14]. These two receptors were found to be extensively co-localized within the cytoplasmic component and plasma membrane of cortical neurons [14]. In contrast, there was much less co-localization of TRPV1 and TRPV2 receptors reported for DRG neurons [14]. Another point of depar-
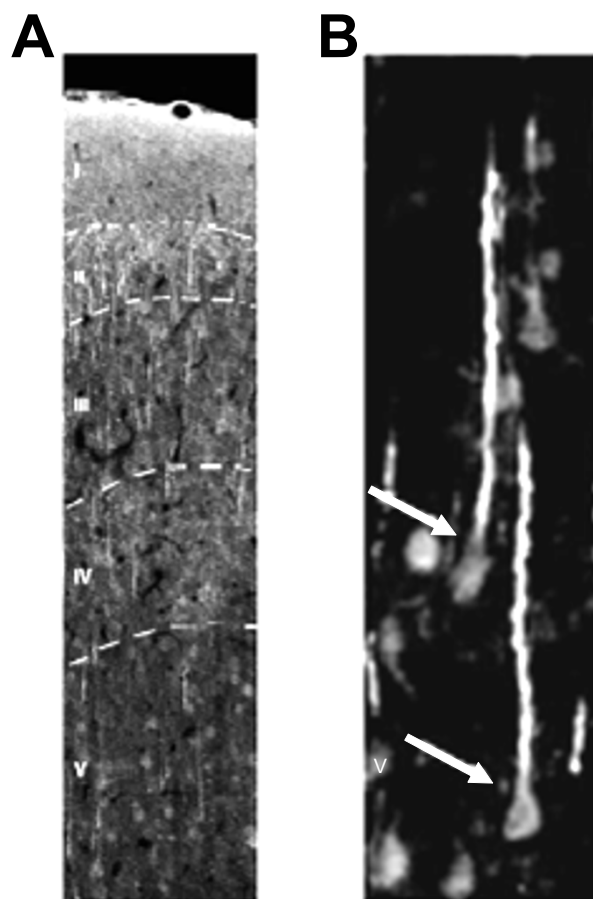

Figure 1
Expression of TRPV1 in the cortex. A. Cortical immunostaining for the TRPV1 receptors in the rat cortex, with each layer indicated (I-V). B. Enlargement of cortical layer V (from A) with arrows indicating pyramidal cells. Reprinted from [19] © 2005 with permission from Elsevier Science.

ture between TRPV1 expression in the DRG and the brain is that, neonatal capsaicin treatment in rats reduces expression of TRPV1 mRNA in the DRG, but not in the brain [16]. The authors suggested that neonatal capsaicin treatment may deplete neurotrophic factors which are required for the survival of peripheral neurons and not central neurons [16]. A more recent finding demonstrated that a high dose of capsaicin to cultured mesencephalic dopaminergic neurons induces cell death [23]. The cell death was likely a consequence of calcium entry leading to mitochondrial damage [23]. Thus capsaicin can destroy central neurons, suggesting that neonatal capsaicin treatments may not reach toxic levels in supraspinal structures.

Since the TRPV1 receptor is activated by capsaicin and is involved in nociceptive processing at the level of the DRG

and sensory nerve endings, it is likely that this receptor occupies a role in pain processing at other brain regions. Such regions might include: the rostral ventromedial medulla, periaqueductal grey, solitary tract nucleus (NTS), preoptic hypothalamus, ventral thalamus, somatosensory cortex, anterior cingulate cortex (ACC), and insula [24,25]. Indeed, the TRPV1 receptor and its mRNA have been localized to neurons in most of these regions (See additional file 1: Table 1.). However, regions such as the NTS appear to express more TRPV1 receptors than that of cingulate or somatosensory cortices. Considering that the expression of DRG TRPV1 receptors can be up-regulated in response to peripheral inflammation [26], it would be of interest to determine whether TRPV1 receptors of the ACC and somatosensory cortex can be similarly regulated.

TRPV1 receptor activation in the brain

The effect of TRPV1 receptor activation in a variety of brain regions has been investigated. These areas include the following: the ventral medulla, periaqueductal grey, solitary tract nucleus (NTS), dorsal raphé nucleus, locus coeruleus, hypothalamus, thalamus, ventral tegmental area, substantia nigra, hippocampus, cerebellum and cortex. Many of these studies have utilized pharmacological activation of TRPV1 receptors with capsaicin. In this section, the effect of TRPV1 receptor activation in the central nervous system will be examined and possible synaptic mechanisms will be addressed.

Ventral medulla

The TRPV1 receptor is involved in the modulation of cardiovascular, respiratory, and temperature control systems at the level of the ventrolateral medulla [27,28]. Microinjection of capsaicin (0.5–50 nmol) into the ventrolateral medulla at the level of the hypoglossal nerve roots was found to increase respiratory output, arterial pressure, and heart rate in an anesthetized rat preparation [27]. Infusion of capsaicin into more caudal regions reduced arterial pressure and heart rate in both anesthetized and chronic rat preparations [27].

Acute systemic administration of capsaicin results in an initial hypothermia, followed by hyperthermia [28-30]. The hypothermia is a result of enhancement of autonomic heat loss mechanisms (e.g. peripheral vasodilation) and a depression of heat saving mechanisms (e.g. shivering) [31]. The latent hyperthermia is likely a result of sympathoadrenal activation [29,32]. Osaka et al. [28] found that lesions of the rostral ventrolateral medulla, a region containing sympathoadrenal preganglionic neurons, largely attenuated capsaicin-induced hyperthermia in anesthetized rats. Consistently, microinjection of capsaicin (500 µmol) into the rostral ventrolateral medulla was found to elicit hyperthermia [28]. The results suggest that capsaicin activates the rostral ventrolateral medulla which

then increases sympathoadrenal activation leading to heat production. It will be of interest to determine whether the actions of capsaicin in this region are specific to the TRPV1 receptor.

Periaqueductal grey

The periaqueductal grey is a well established component of the pain modulatory circuitry and projects to the rostral ventromedial medulla [25,33]. The rostral ventromedial medulla can subsequently exert descending modulation over nociceptive spinal reflex pathways [33-37]. Palazzo et al. [38] demonstrated that capsaicin injection (1–6 nmol) at the periaqueductal grey can increase the latency of nociceptive responses, indicating analgesia. This effect could be blocked by local antagonism of NMDA and metabotropic glutamate receptors. In contrast, McGaraughty et al. [39] found that capsaicin (10 nmol) injected into the dorsal periaqueductal grey could decrease the latency of both nociceptive behavioral responses and rostral ventromedial medulla tail-flick-on cell activity, suggesting hyperalgesia. To account for this discrepancy, McGaraughty et al. [39] suggested that the fast delivery of capsaicin by Palazzo et al. [38] may have desensitized the TRPV1 receptors resulting in analgesia.

A recent investigation by Maione et al. [40] demonstrated that elevation of endocannabinoid levels, with an inhibitor of fatty acid amide hydrolase, in the ventrolateral periaqueductal grey can produce analgesia and hyperalgesia. This effect was shown to be dependent on the activation of TRPV1 and CB1 (cannabinoid receptor-1) receptors. Low doses of inhibitor at the periaqueductal grey produced rapid hyperalgesia. The hyperalgesia was proposed to result from an increase in 2-arachidonoylglycerol, which stimulates CB1 receptors preferentially over TRPV1 receptors [40]. This leads to descending inhibition of off-cells and stimulates on-cells in the rostral ventromedial medulla, speeding up nociceptive responses [40]. Higher doses of fatty acid amide inhibitor cause rapid analgesia followed by a delayed hyperalgesia [40]. The findings were explained by suggesting that anandamide levels increase and stimulate TRPV1 receptors resulting in analgesia. Subsequently, 2-arachidonoylglycerol levels increase to stimulate CB1 receptors resulting in hyperalgesia. Again, the effects of the inhibitor at the periaqueductal grey would be mediated through descending modulation of the appropriate rostral ventromedial medulla circuitry [40]. Consistent with the concept that these two receptors modulate descending facilitatory and inhibitory output to the rostral ventromedial medulla, Maione et al. [40] found that some neurons of the periaqueductal grey co-expressed TRPV1 and CB1 receptors.

Nucleus of the solitary tract

Activation of TRPV1 receptors in the NTS has been found to induce hypotension, bradycardia [41], and reduction of respiratory rate [42]. In-vitro brainstem slice experiments demonstrated that acute capsaicin (100 nM) treatment induces a rapidly developing inward current in NTS neurons. Capsaicin treatment also enhanced spontaneous glutamatergic currents [43]. The effects of the capsaicin treatment were restricted to a subpopulation of NTS neurons [43]. Additional evidence suggested that the capsaicin was acting on presynaptic TRPV1 receptors to enhance glutamate release onto AMPA receptors [43]. In addition, capsaicin sensitive neurons of the NTS, but not insensitive neurons, can be characterized by large transient outward currents [44]. The results suggest that within a particular brain region, activation of TRPV1 receptors may selectively affect neurons characterized by distinct electrophysiological properties.

Dorsal raphé nucleus

Peripheral administration of capsaicin results in bursting activity in the dorsal raphé nucleus, recorded with intracortical electroencephalogram in rats [45]. In addition, direct injection of capsaicin (65 nmol) into the dorsal raphé nucleus increases vasodilation of the skin and decreases core body temperature in anesthetized rats [46].

Locus coeruleus

The locus coeruleus is activated by painful stimuli and is involved in the production of antinociception [33,47]. Intravenous administration of capsaicin increases firing rates of locus coeruleus neurons in anesthetized rats [48]. This increased firing even occurred following neonatal capsaicin treatment to destroy sensory nerve fibers, indicating a central effect of capsaicin [48]. Consistent with this excitatory effect, TRPV1 activation at the locus coeruleus with capsaicin (1 μM) was found to enhance glutamatergic miniature excitatory postsynaptic currents through a presynaptic mechanism [49].

Hypothalamus

Injection of capsaicin (2–80 nmol) into the preoptic area of the hypothalamus causes an abrupt hypothermic response [50], and increases the activity of warm-sensitive neurons while depressing the activity of cold-sensitive neurons [30]. In addition, capsaicin (~4 μM) can evoke glutamate release in rat hypothalamic slice preparations [13,22] and enhance postsynaptic currents [51] (Fig. 2).

Thalamus

Nociceptive (pinch sensitive) neurons in the medial thalamus can be activated by arterial capsaicin infusion [52-54], an effect that can be blocked by morphine [54]. Interestingly, TRPV1 gene knockout mice are not impaired in the detection of noxious mechanical stimuli as deter-
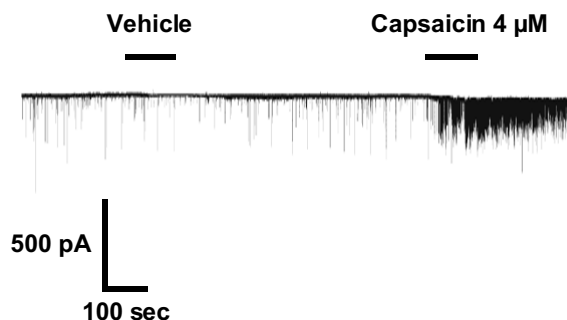
Vehicle   **Capsaicin 4 μM**

500 pA

100 sec

Figure 2
TRPV1 modulates synaptic events in the hypothalamus. Activation of TRPV1 receptors increases the frequency of postsynaptic currents of hypothalamic medial preoptic nucleus neurons studied in-vitro. Reprinted from [51] © 2005 with permission from Elsevier Science.

mined by tail pinch, von-Frey test, and spinal nociceptive neuron responses [12]. However, this does not rule out the possibility that thalamic TRPV1 receptors modulate noxious mechanical information once it has been detected.

Ventral tegmental area

Application of capsaicin (1–10 μM) to the ventral tegmental area increases the firing rate and bursting activity of dopaminergic neurons in-vitro [55] (Fig. 3). In addition, it was shown that activation of TRPV1 receptors of the ventral tegmental area could enhance dopaminergic output to the nucleus accumbens, following peripheral noxious stimulation [55].

Substantia nigra

Peripheral administration of capsaicin results in bursting activity in the substantia nigra, recorded with intracortical electroencephalogram in rats [45]. Injection of capsaicin into the substantia nigra can enhance locomotor behaviors (100 nmol capsaicin) and produce peripheral vasodilation (30–100 nmol capsaicin) [56,57]. In-vitro studies have demonstrated that TRPV1 activation (1–10 μM capsaicin) enhances glutamatergic synaptic transmission to dopaminergic neurons of the substantia nigra [58]. In addition, analysis of excitatory postsynaptic currents suggested a presynaptic mechanism for this enhancement [58]. Importantly, this study demonstrated that TRPV1 is activated by endogenous ligands in-vitro, since antagonism of the receptor reduced the frequency of spontaneous excitatory postsynaptic currents.
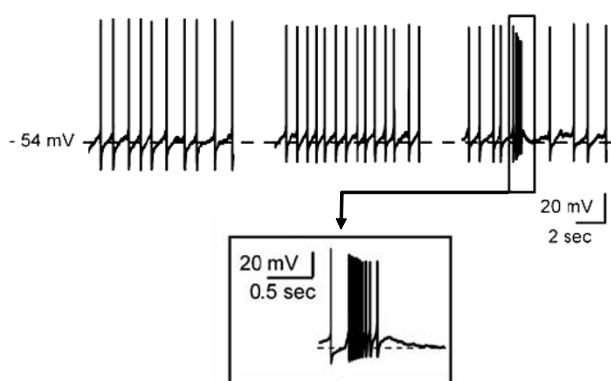
Figure 3
TRPV1 modulates spike activity of ventral tegmental area. Dopamine cell recorded in whole cell current clamp mode in-vitro slice preparation. Bath application of capsaicin (middle trace) augmented firing frequency of ventral tegmental cells. In some cases bursting activity was observed (rightmost trace and inset). Inset also shows action potentials superimposed on depolarizing envelope. These results indicate that TRPV1 activation can directly modulate central neurons. Adapted from [55] © 2005 with permission from Macmillan Publishers Ltd.

Hippocampus

In the hippocampal CA1 region, TRPV1 activation enhances paired-pulse depression [7,59]. It is possible that the mechanism of the depression was the activation of presynaptic TRPV1 receptors at GABAergic terminals, which feed back and inhibit CA1 neurons [59,60]. This would be expected to have the net effect of increasing GABA output [60]. However, TRPV1 receptor activation was found to inhibit the influx of calcium and reduce GABA release in synaptosomal hippocampus preparations [60]. This discrepancy between in-vitro and ex-vivo data may be a consequence of the disruption of intracellular or extracellular molecules under ex-vivo conditions. These molecules may modulate TRPV1 receptor function. Alternatively, the discrepancy may be due to rapid desensitization of TRPV1 receptors under ex-vivo conditions [60].

Cerebellum

Microiontophoretically applied capsaicin into the cerebellum depresses neuron spike activity [61]. This finding is interesting because it differs from the excitatory effect of capsaicin in other regions of the brain. In contrast with the hypothalamus and cerebral cortex (below), activation of the TRPV1 receptor does not evoke glutamate release in cerebellum tissue slices [13].

Cortex

The somatosensory cortex and ACC are both involved in the processing of pain [24,25,33,62]. However, few studies have examined the effect of direct TRPV1 receptor activation in these regions. It has been shown that activation of the TRPV1 receptor can evoke glutamate release from cortical slices [13]. In addition, a study by Toldi et al. [63] showed that local application of capsaicin to the somatosensory cortex reduced mechanically and electrically evoked potentials of anesthetized rats [63].

Preliminary in-vitro data from our laboratory show that capsaicin application (50 μM) to the ACC increases the firing frequency of some neurons (Fig. 4), while depressing firing of other neurons. The differing direction of neuron firing patterns is similar to the effects observed in the hypothalamic preoptic area [30]. Since the ACC is involved in the formation of pain-associated memory and the descending modulation of nociception [64,65], it will be of interest to determine whether or not the TRPV1 receptor can influence these processes.

Future directions

The TRPV1 receptor is expressed and functional throughout the brain. It is possible that populations of TRPV1 receptors within the brain are also involved in processing nociceptive information. This not only suggests that local manipulation of cortical TRPV1 may lead to alterations in pain behaviors, but also warns against assigning a strictly peripheral role of TRPV1 receptors in pain transmission. For example, since TRPV1 receptor knockout mice have a global gene deletion, it is not possible to discount the role of the receptors expressed at supraspinal structures in the pain phenotypes reported [12].

The most prominent expression of TRPV1 mRNA and receptors is in the DRG with expression much less concentrated in supraspinal structures. While, minor expression does not necessarily imply minor functions, research will need to carefully examine the role of the TRPV1 receptors in the brain. Indeed, many early studies were conducted without determining the specificity of the capsaicin effect to the TRPV1 receptor. Future experimentation will need to confirm the involvement of TRPV1 receptors in the brain with antagonists and TRPV1-deficient mouse studies.

Electrophysiological studies indicate that the actions of the TRPV1 receptor in supraspinal structures are largely presynaptic [13,22,43,49,58]. However, this receptor is reported to be localized to postsynaptic spines in the brain [19]. This inconsistency is likely due to incomplete analysis of synaptic TRPV1 localization throughout the whole brain.
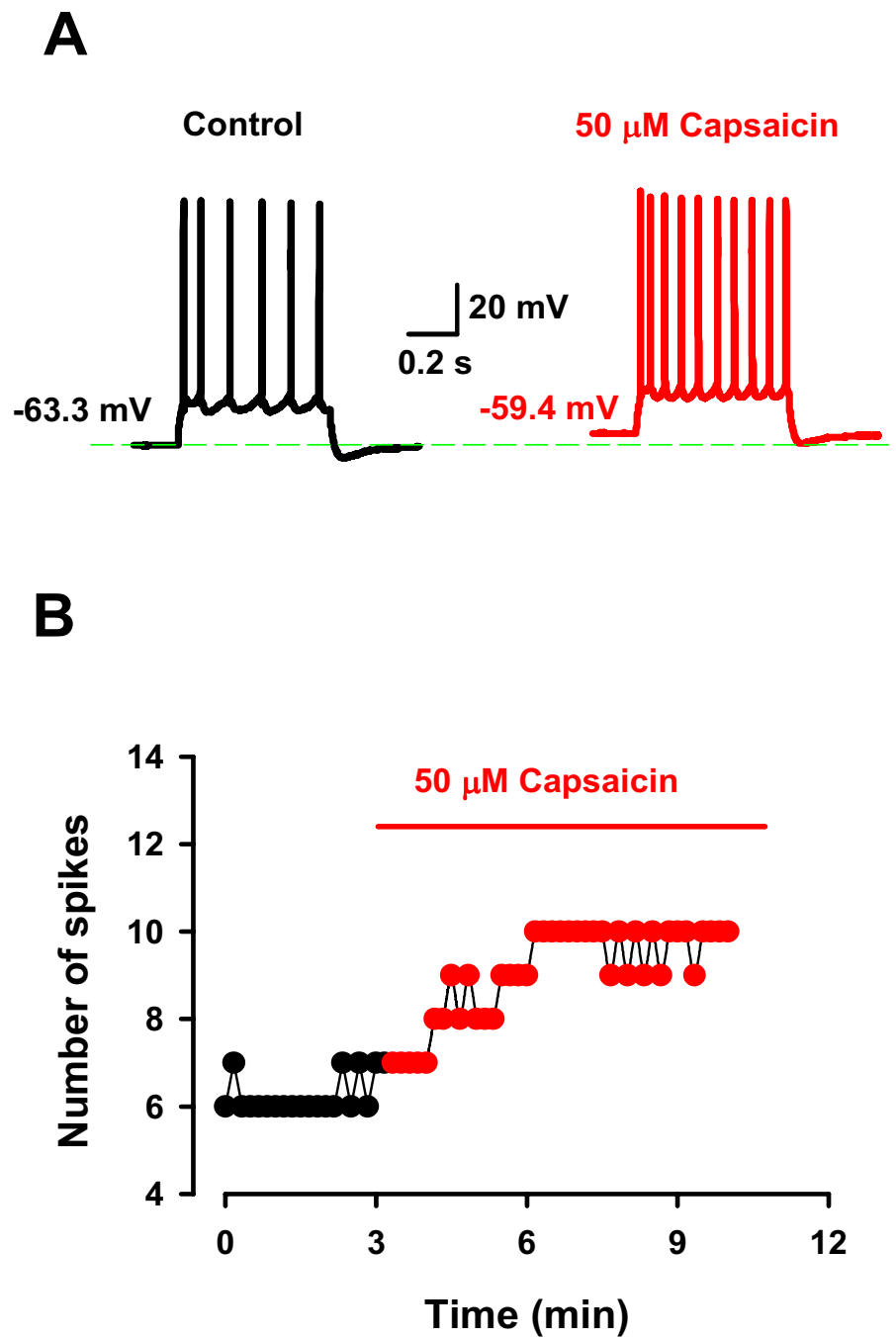
A

Figure 4
Capsaicin activates anterior cingulate cortex neurons. A. Current injection (220 pA, 800 ms) into a pyramidal neuron in layer II-III in the ACC induced action potential firing. Perfusion of capsaicin (50 μM) significantly increased the number of spikes. Note the slight depolarizing effect of capsaicin in the neuron (dashed line). The results indicate that TRPV1 receptors are functional in a cortical brain region involved in pain processing. B. Time course of capsaicin effect on the neuron shown in A

Direct activation of the TRPV1 receptor in different brain regions can result in diverse effects including changes in body temperature, respiration, heart rate, blood pressure and locomotion [27,28,41,42,46,50,56,57]. This indicates that TRPV1 receptor function depends on where it is located in the brain.

The TRPV1 receptor is not only of interest to the basic neuroscientist but also among pharmaceutical industries. The initial observation that there was little or no expression of this receptor in the brain suggested that this receptor would be an ideal target for the treatment of pain. Although treating pain through the modulation of the TRPV1 receptor is an exciting prospect, caution should be exercised when developing drugs to target this receptor since it is expressed and functional in the brain [3,14-21] and body [6,13]. More extensive research of supraspinal TRPV1 receptors is needed to determine its role in synaptic transmission and the control of behavior.

Abbreviations
ACC Anterior cingulate cortex

ATP Adenosine triphosphate

DRG Dorsal root ganglion

NTS Solitary tract nucleus

TRPV1 Transient receptor potential vanilloid-1

CB1 Cannabinoid receptor-1

Competing interests
The author(s) declare that they have no competing interests.

Additional material

Additional File 1
TRPV1 detection in the brain. TRPV1 can be detected in the brain using a variety of methodologies. Abbreviations as follows: d, detected but intensity not reported; [^{3}H]RTX resiniferatoxin binding; IH, immunohistochemistry; ISH, in-situ hybridization; NB, northern blot, nd, not detected; RPA, ribonuclease protection assay; RT-PCR, reverse transcription polymerase chain reaction; WB, western blot; * to ***, relative intensity of detection; References are indicated at the top of each column.
Click here for file
[http://www.biomedcentral.com/content/supplementary/1744-8069-2-34-S1.doc]

References
1. Tominaga M, Caterina MJ, Malmberg AB, Rosen TA, Gilbert H, Skinner K, Raumann BE, Basbaum AI, Julius D: **The cloned capsaicin receptor integrates multiple pain-producing stimuli.** *Neuron* 1998, **21:**531-543.
2. Davis JB, Gray J, Gunthorpe MJ, Hatcher JP, Davey PT, Overend P, Harries MH, Latcham J, Clapham C, Atkinson K, Hughes SA, Rance K, Grau E, Harper AJ, Pugh PL, Rogers DC, Bingham S, Randall A, Sheardown SA: **Vanilloid receptor-1 is essential for inflammatory thermal hyperalgesia.** *Nature* 2000, **405:**183-187.
3. Caterina MJ, Schumacher MA, Tominaga M, Rosen TA, Levine JD, Julius D: **The capsaicin receptor: a heat-activated ion channel in the pain pathway.** *Nature* 1997, **389:**816-824.
4. Tominaga M, Tominaga T: **Structure and function of TRPV1.** *Pflugers Arch* 2005, **451:**143-150.
5. Tominaga M, Caterina MJ: **Thermosensation and pain.** *J Neurobiol* 2004, **61:**3-12.
6. Nagy I, Santha P, Jancso G, Urban L: **The role of the vanilloid (capsaicin) receptor (TRPV1) in physiology and pathology.** *Eur J Pharmacol* 2004, **500:**351-369.
7. Huang SM, Bisogno T, Trevisani M, Al-Hayani A, De Petrocellis L, Fezza F, Tognetto M, Petros TJ, Krey JF, Chu CJ, Miller JD, Davies SN, Geppetti P, Walker JM, Di Marzo V: **An endogenous capsaicin-like substance with high potency at recombinant and native vanilloid VR1 receptors.** *Proc Natl Acad Sci U S A* 2002, **99:**8400-8405.
8. Prescott ED, Julius D: **A modular PIP2 binding site as a determinant of capsaicin receptor sensitivity.** *Science* 2003, **300:**1284-1288.
9. Smith GD, Gunthorpe MJ, Kelsell RE, Hayes PD, Reilly P, Facer P, Wright JE, Jerman JC, Walhin JP, Ooi L, Egerton J, Charles KJ, Smart D, Randall AD, Anand P, Davis JB: **TRPV3 is a temperature-sensitive vanilloid receptor-like protein.** *Nature* 2002, **418:**186-190.
10. Vennekens R, Voets T, Bindels RJ, Droogmans G, Nilius B: **Current understanding of mammalian TRP homologues.** *Cell Calcium* 2002, **31:**253-264.
11. Morenilla-Palao C, Planells-Cases R, Garcia-Sanz N, Ferrer-Montiel A: **Regulated exocytosis contributes to protein kinase C potentiation of vanilloid receptor activity.** *J Biol Chem* 2004, **279:**25665-25672.
12. Caterina MJ, Leffler A, Malmberg AB, Martin WJ, Trafton J, Petersen-Zeitz KR, Koltzenburg M, Basbaum AI, Julius D: **Impaired nociception and pain sensation in mice lacking the capsaicin receptor.** *Science* 2000, **288:**306-313.
13. Sasamura T, Kuraishi Y: **Peripheral and central actions of capsaicin and VR1 receptor.** *Jpn J Pharmacol* 1999, **80:**275-280.
14. Liapi A, Wood JN: **Extensive co-localization and heteromultimer formation of the vanilloid receptor-like protein TRPV2 and the capsaicin receptor TRPV1 in the adult rat cerebral cortex.** *Eur J Neurosci* 2005, **22:**825-834.
15. Szallasi A, Nilsson S, Farkas-Szallasi T, Blumberg PM, Hokfelt T, Lundberg JM: **Vanilloid (capsaicin) receptors in the rat: distribution in the brain, regional differences in the spinal cord, axonal transport to the periphery, and depletion by systemic vanilloid treatment.** *Brain Res* 1995, **703:**175-183.
16. Mezey E, Toth ZE, Cortright DN, Arzubi MK, Krause JE, Elde R, Guo A, Blumberg PM, Szallasi A: **Distribution of mRNA for vanilloid receptor subtype 1 (VR1), and VR1-like immunoreactivity, in the central nervous system of the rat and human.** *Proc Natl Acad Sci U S A* 2000, **97:**3655-3660.
17. Acs G, Palkovits M, Blumberg PM: **Specific binding of [3H]resiniferatoxin by human and rat preoptic area, locus ceruleus, medial hypothalamus, reticular formation and ventral thalamus membrane preparations.** *Life Sci* 1996, **59:**1899-1908.
18. Roberts JC, Davis JB, Benham CD: **[3H]Resiniferatoxin autoradiography in the CNS of wild-type and TRPV1 null mice defines TRPV1 (VR-1) protein distribution.** *Brain Res* 2004, **995:**176-183.
19. Toth A, Boczan J, Kedei N, Lizanecz E, Bagi Z, Papp Z, Edes I, Csiba L, Blumberg PM: **Expression and distribution of vanilloid receptor 1 (TRPV1) in the adult rat brain.** *Brain Res Mol Brain Res* 2005, **135:**162-168.
20. Szabo T, Biro T, Gonzalez AF, Palkovits M, Blumberg PM: **Pharmacological characterization of vanilloid receptor located in the brain.** *Brain Res Mol Brain Res* 2002, **98:**51-57.
21. Sanchez JF, Krause JE, Cortright DN: **The distribution and regulation of vanilloid receptor VR1 and VR1 5' splice variant RNA expression in rat.** *Neuroscience* 2001, **107:**373-381.

22. Sasamura T, Sasaki M, Tohda C, Kuraishi Y: **Existence of capsaicin-sensitive glutamatergic terminals in rat hypothalamus.** *Neuroreport* 1998, **9:**2045-2048.

23. Kim SR, Lee DY, Chung ES, Oh UT, Kim SU, Jin BK: **Transient receptor potential vanilloid subtype 1 mediates cell death of mesencephalic dopaminergic neurons in vivo and in vitro.** *J Neurosci* 2005, **25:**662-671.

24. Millan MJ: **Descending control of pain.** *Prog Neurobiol* 2002, **66:**355-474.

25. Millan MJ: **The induction of pain: an integrative review.** *Prog Neurobiol* 1999, **57:**1-164.

26. Ji RR, Samad TA, Jin SX, Schmoll R, Woolf CJ: **p38 MAPK activation by NGF in primary sensory neurons after inflammation increases TRPV1 levels and maintains heat hyperalgesia.** *Neuron* 2002, **36:**57-68.

27. Koulchitsky SV, Azev OA, Gourine AV, Kulchitsky VA: **Capsaicin-sensitive area in the ventral surface of the rat medulla.** *Neurosci Lett* 1994, **182:**129-132.

28. Osaka T, Lee TH, Kobayashi A, Inoue S, Kimura S: **Thermogenesis mediated by a capsaicin-sensitive area in the ventrolateral medulla.** *Neuroreport* 2000, **11:**2425-2428.

29. Kobayashi A, Osaka T, Namba Y, Inoue S, Lee TH, Kimura S: **Capsaicin activates heat loss and heat production simultaneously and independently in rats.** *Am J Physiol* 1998, **275:**R92-8.

30. Hori T, Shibata M, Kiyohara T, Nakashima T, Asami A: **Responses of anterior hypothalamic-preoptic thermosensitive neurons to locally applied capsaicin.** *Neuropharmacology* 1988, **27:**135-142.

31. Hori T: **Capsaicin and central control of thermoregulation.** *Pharmacol Ther* 1984, **26:**389-416.

32. Watanabe T, Kawada T, Kurosawa M, Sato A, Iwai K: **Adrenal sympathetic efferent nerve and catecholamine secretion excitation caused by capsaicin in rats.** *Am J Physiol* 1988, **255:**E23-7.

33. Renn CL, Dorsey SG: **The physiology and processing of pain: a review.** *AACN Clin Issues* 2005, **16:**277-90; quiz 413-5.

34. Zhuo M, Gebhart GF: **Facilitation and attenuation of a visceral nociceptive reflex from the rostroventral medulla in the rat.** *Gastroenterology* 2002, **122:**1007-1019.

35. Zhuo M, Sengupta JN, Gebhart GF: **Biphasic modulation of spinal visceral nociceptive transmission from the rostroventral medial medulla in the rat.** *J Neurophysiol* 2002, **87:**2225-2236.

36. Zhuo M, Gebhart GF: **Modulation of noxious and non-noxious spinal mechanical transmission from the rostral medial medulla in the rat.** *J Neurophysiol* 2002, **88:**2928-2941.

37. Gebhart GF: **Descending modulation of pain.** *Neurosci Biobehav Rev* 2004, **27:**729-737.

38. Palazzo E, de Novellis V, Marabese I, Cuomo D, Rossi F, Berrino L, Maione S: **Interaction between vanilloid and glutamate receptors in the central modulation of nociception.** *Eur J Pharmacol* 2002, **439:**69-75.

39. McGaraughty S, Chu KL, Bitner RS, Martino B, El Kouhen R, Han P, Nikkel AL, Burgard EC, Faltynek CR, Jarvis MF: **Capsaicin infused into the PAG affects rat tail flick responses to noxious heat and alters neuronal firing in the RVM.** *J Neurophysiol* 2003, **90:**2702-2710.

40. Maione S, Bisogno T, de Novellis V, Palazzo E, Cristino L, Valenti M, Petrosino S, Guglielmotti V, Rossi F, Di Marzo V: **Elevation of endocannabinoid levels in the ventrolateral periaqueductal grey through inhibition of fatty acid amide hydrolase affects descending nociceptive pathways via both cannabinoid receptor type 1 and transient receptor potential vanilloid type-1 receptors.** *J Pharmacol Exp Ther* 2006, **316:**969-982.

41. Lukovic L, de Jong W, de Wied D: **Cardiovascular effects of substance P and capsaicin microinjected into the nucleus tractus solitarii of the rat.** *Brain Res* 1987, **422:**312-318.

42. Geraghty DP, Mazzone SB: **Respiratory actions of vanilloid receptor agonists in the nucleus of the solitary tract: comparison of resiniferatoxin with non-pungent agents and anandamide.** *Br J Pharmacol* 2002, **137:**919-927.

43. Doyle MW, Bailey TW, Jin YH, Andresen MC: **Vanilloid receptors presynaptically modulate cranial visceral afferent synaptic transmission in nucleus tractus solitarius.** *J Neurosci* 2002, **22:**8222-8229.

44. Bailey TW, Jin YH, Doyle MW, Andresen MC: **Vanilloid-sensitive afferents activate neurons with prominent A-type potassium currents in nucleus tractus solitarius.** *J Neurosci* 2002, **22:**8230-8237.

45. Rabe LS, Buck SH, Moreno L, Burks TF, Dafny N: **Neurophysiological and thermoregulatory effects of capsaicin.** *Brain Res Bull* 1980, **5:**755-758.

46. Hajos M, Hjorth S, Carlsson A: **Injection of capsaicin into the nucleus raphe dorsalis elicits heat loss in the rat.** *Neurosci Lett* 1987, **75:**199-204.

47. Singewald N, Philippu A: **Release of neurotransmitters in the locus coeruleus.** *Prog Neurobiol* 1998, **56:**237-267.

48. Hajos M, Jancso G, Engberg G: **Capsaicin-induced excitation of locus coeruleus neurons.** *Acta Physiol Scand* 1987, **129:**415-420.

49. Marinelli S, Vaughan CW, Christie MJ, Connor M: **Capsaicin activation of glutamatergic synaptic transmission in the rat locus coeruleus in vitro.** *J Physiol* 2002, **543:**531-540.

50. Jancso-Gabor A, Szolcsanyi J, Jancso N: **Stimulation and desensitization of the hypothalamic heat-sensitive structures by capsaicin in rats.** *J Physiol* 1970, **208:**449-459.

51. Karlsson U, Sundgren-Andersson AK, Johansson S, Krupp JJ: **Capsaicin augments synaptic transmission in the rat medial preoptic nucleus.** *Brain Res* 2005, **1043:**1-11.

52. Andoh R, Shima K, Miyagawa T, Sakurada S, Kisara K, Ohsawa K, Takahashi M: **Excitatory effects of dihydrocapsaicin on nociceptive neurons in the medial thalamus.** *Jpn J Pharmacol* 1980, **30:**599-605.

53. Andoh R, Sakurada S, Sato T, Takahashi N, Kisara K: **Potentiating effects of prostaglandin E2 on bradykinin and capsaicin responses in medial thalamic nociceptive neurons.** *Jpn J Pharmacol* 1982, **32:**81-89.

54. Ando R, Onodera K, Shima K, Kisara K: **[Effects of capsaicin on spontaneous unit discharges in medial thalamic single neurons of cats (author's transl)].** *Nippon Yakurigaku Zasshi* 1977, **73:**955-959.

55. Marinelli S, Pascucci T, Bernardi G, Puglisi-Allegra S, Mercuri NB: **Activation of TRPV1 in the VTA excites dopaminergic neurons and increases chemical- and noxious-induced dopamine release in the nucleus accumbens.** *Neuropsychopharmacology* 2005, **30:**864-870.

56. Dawbarn D, Harmar AJ, Pycock CJ: **Intranigral injection of capsaicin enhances motor activity and depletes nigral 5-hydroxytryptamine but not substance P.** *Neuropharmacology* 1981, **20:**341-346.

57. Hajos M, Engberg G, Nissbrandt H, Magnusson T, Carlsson A: **Capsaicin-sensitive vasodilatatory mechanisms in the rat substantia nigra and striatum.** *J Neural Transm* 1988, **74:**129-139.

58. Marinelli S, Di Marzo V, Berretta N, Matias I, Maccarrone M, Bernardi G, Mercuri NB: **Presynaptic facilitation of glutamatergic synapses to dopaminergic neurons of the rat substantia nigra by endogenous stimulation of vanilloid receptors.** *J Neurosci* 2003, **23:**3136-3144.

59. Al-Hayani A, Wease KN, Ross RA, Pertwee RG, Davies SN: **The endogenous cannabinoid anandamide activates vanilloid receptors in the rat hippocampal slice.** *Neuropharmacology* 2001, **41:**1000-1005.

60. Kofalvi A, Oliveira CR, Cunha RA: **Lack of evidence for functional TRPV(1) vanilloid receptors in rat hippocampal nerve terminals.** *Neurosci Lett* 2006.

61. Salt TE, Hill RG: **The effects of microiontophoretically applied capsaicin and substance P on single neurones in the rat and cat brain.** *Neurosci Lett* 1980, **20:**329-334.

62. Zhuo M: **Canadian Association of Neuroscience review: Cellular and synaptic insights into physiological and pathological pain. EJLB-CIHR Michael Smith Chair in Neurosciences and Mental Health lecture.** *Can J Neurol Sci* 2005, **32:**27-36.

63. Toldi J, Joo F, Wolfe JR: **Capsaicin differentially influences somatosensory cortical responses evoked by peripheral electrical or mechanical stimulation.** *Neuroscience* 1992, **49:**135-139.

64. Calejesan AA, Kim SJ, Zhuo M: **Descending facilitatory modulation of a behavioral nociceptive response by stimulation in the adult rat anterior cingulate cortex.** *Eur J Pain* 2000, **4:**83-96.

65. Tang J, Ko S, Ding HK, Qiu CS, Calejesan AA, Zhuo M: **Pavlovian fear memory induced by activation in the anterior cingulate cortex.** *Mol Pain* 2005, **1:**6.