Cell Tissue Res (2005) 322: 201–206
DOI 10.1007/s00441-005-0004-4

REGULAR ARTICLE

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Distribution of TRPC1 and TRPC5 in medial temporal lobe structures of mice

Received: 18 March 2005 / Accepted: 10 May 2005 / Published online: 26 July 2005

Abstract The transient receptor potential (TRP) superfamily comprises a group of non-selective cation channels that have been implicated in both receptor and store-operated channel functions. The family of the classical TRPs (TRPCs) consists of seven members (TRPC1-7). The presence of TRPC1 and TRPC5 mRNA in the brain has previously been demonstrated by real-time polymerase chain reaction. However, the distribution of these receptors within different brain areas of mice has not been investigated in detail. We have used antibodies directed against TRPC1 and TRPC5 to study the distribution and localization of these channels in murine medial temporal lobe structures. Both TRPC1 and TRPC5 channels are present in the various nuclei of the amygdala, in the hippocampus, and in the subiculum and the entorhinal cortex. We have found that TRPC1 channels are primarily expressed on cell somata and on dendrites, whereas TRPC5 channels are exclusively located on cell bodies. Moreover, TRPC1 channels are selectively expressed by neurons, whereas TRPC5 channels are mainly expressed by neurons, but also by non-neuronal cells. The expression of TRPC1 and TRPC5 channels in mammalian temporal lobe structures suggests their involvement in neuronal plasticity, learning and memory.

Keywords Transient receptor potential superfamily · Immunohistochemistry · Hippocampus · Entorhinal cortex · Subiculum · Amygdala · Mouse (C57/Bl6)

This work was supported by the DFG (SFB 636/A5).

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Introduction

The transient receptor potential (TRP) superfamily comprises a group of non-selective cation channels that is expressed in many tissues and cell types. TRP channels represent a diverse group of proteins organized into six families: the classical TRPs (TRPCs), the vanilloid receptor TRPs (TRPVs), the melastatin or long TRPs (TRPMs), the mucolipins (TRPMLs), the polycystins (TRPPs) and ankyrin transmembrane protein 1 (ANKTM1 or TRPA1; Huang 2004; Moran et al. 2004).

The family of TRPCs consists of seven members (TRPC1-7) that are activated subsequent to receptor-mediated stimulation of the different isoforms of phospholipase C (Harteneck et al. 2000). Mammalian TRPC family members are putative receptor- and store-operated cation channels that play an essential role in cellular calcium homeostasis (Strubing et al. 2001). TRPC channels are thought to be tetrameric and increasing evidence suggests heteromultimeric channel assembly. Therefore, the assembly of the TRPC family members into homo- and heteromers can create a variety of different channels. However, not all TRPC channels form heteromers; for example, TRPC2 does not seem to interact with any known TRPC protein (Hofmann et al. 2002). TRPC1 can form channel complexes with TRPC4 and TRPC5, and all other TRPCs assemble exclusively into homomers or heteromers within the TRPC superfamilies (TRPC4/5 or TRPC3/6/7; Hofmann et al. 2002). However, the channel subunit composition in vivo and the mechanisms underlying subunit assembly are still largely unknown (Schilling and Goel 2004).

Communication via calcium signals between cells is known to be operative between neurons in which these signals are integrated intimately with electrical and chemical signal cross-talk at synapses (Braet et al. 2004). Thus, TRP channels may play an important role in neuronal communication. Despite this putative role, little is known about their distribution in the adult brain. The expression of TRPC1, TRPC3, TRPC4, TRPC5, TRPC6 and TRPC7 mRNA and protein has been observed in proliferating cells of the rat-derived hippocampal H19-7 cell line (Wu et al.

2004). By using quantitative real-time polymerase chain reaction (RT-PCR), the presence of TRPC mRNA has been detected in the adult human brain, and TRPC1, TRPC4, TRPC5 and TRPC6 mRNAs have been detected in the hippocampus and amygdala (Riccio et al. 2002). In another study, only TRPC1, TRPC4 and TRPC5 proteins have been detected in the adult rat brain by Western blot analysis (Strubing et al. 2003). In situ hybridization has mapped TRPC4 (Mori et al. 1998) and TRPC7 (Okada et al. 1999) mRNAs to the murine hippocampus. TRPC3, however, seems only to occur at prenatal but not at postnatal stages in the hippocampus, at least in rats (Li et al. 1999). The significance of these expression profiles is difficult to assess, since mRNA levels do not necessarily reflect the relative abundance of the protein and do not allow conclusions to be drawn concerning their distribution.

The amygdala and the hippocampal formation are critically involved in memory processing (Izquierdo and Medina 1993; Miller et al. 1998) and calcium-dependent synaptic plasticity has been demonstrated in these structures (Foster 1999; Wang and Gean 1999). In this study, we have used specific affinity-purified antibodies against TRPC1 and TRPC5 to investigate the distribution of these channels in these medial temporal lobe structures of mice.

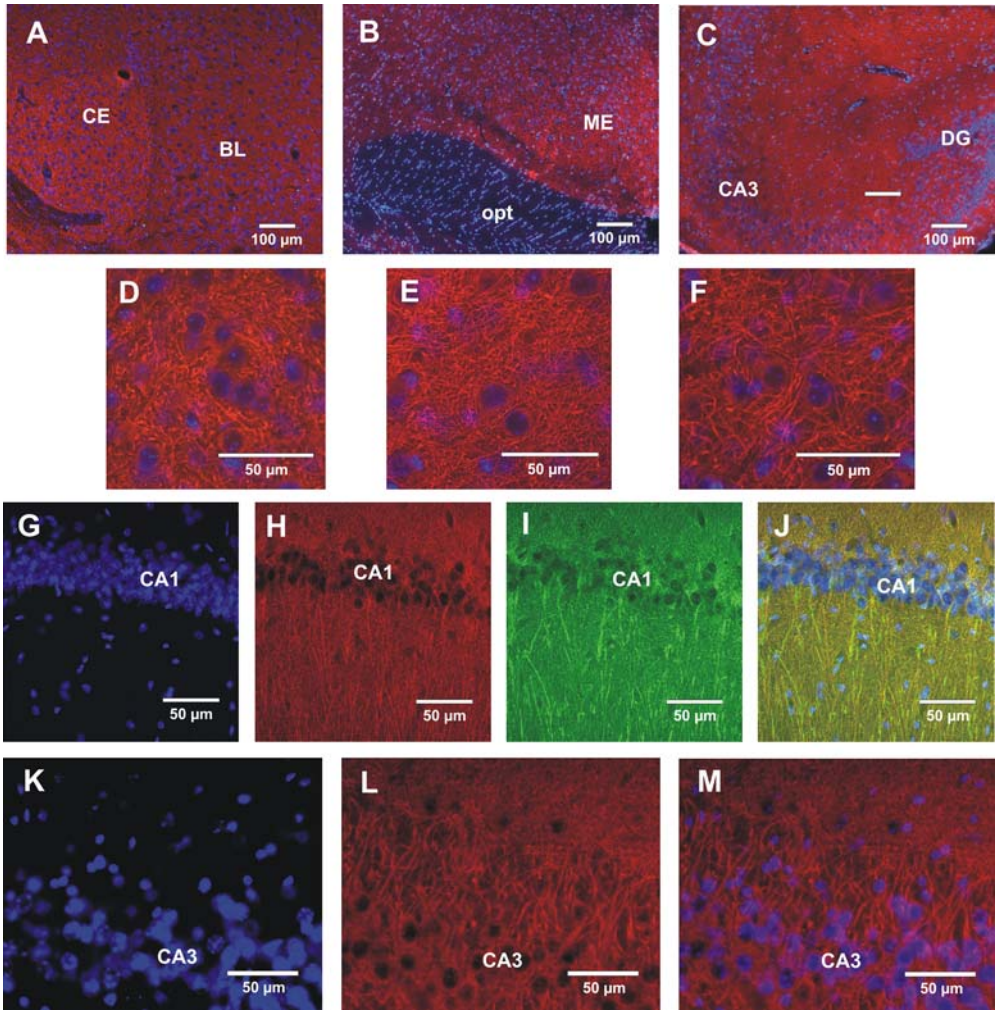

Fig. 1 Micrographs of anti-TRPC1-stained material. **a** TRPC1 immunoreactivity (*red*) was found in the basolateral nucleus (*BL*) and central nucleus (*CE*) of the amygdala. The staining was mainly found on fibres. Note that the staining intensities were higher in the CE than in the BL. Coronal section, counterstained with DAPI (*blue*). **b** TRPC1 immunoreactivity (*red*) was mainly located in fibres of the medial nucleus (*ME*) of the amygdala, whereas TRPC1 staining was absent in the optic tract (*opt*). Horizontal section, counterstained with DAPI (*blue*). **c** Overview of the TRPC1 immunoreactivity (*red*) in the hippocampal formation (*CA3* hippocampal field CA3, *DG* dentate gyrus). Again, TRPC1 immunoreactivity was mainly found in fibres. Horizontal section, counterstained with DAPI (*blue*). **d** TRPC1 immunoreactivity (*red*) in the CE at a higher magnification. Coronal section, counterstained with DAPI (*blue*). **e** TRPC1 immunoreactivity (*red*) in the BL at a higher magnification. Coronal section, counterstained with DAPI (*blue*). **f** TRPC1 immunoreactivity (*red*) in the ME at a higher magnification. Horizontal section, counterstained with DAPI (*blue*). **g** DAPI-stained cells in the hippocampal field CA1. Coronal section. **h** TRPC1 immunoreactivity (*red*) in area CA1 of the hippocampus (same section as in **g**). **i** Same section as in **g**, **h**. The *green* fluorescence is indicative of the immuno-signal of MAP2, a dendritic marker. **j** Overlay of **g-i** showing that TRPC1 immunoreactivity is co-localized with the MAP2-signal. **k** DAPI-stained cells in hippocampal field CA3. Coronal section. **l** Same section as in **k** displaying TRPC1 immunoreactivity. **m** Overlay of **k**, **l**

Materials and methods

Adult (6 months old) C57/Bl6 mice (n=5) were used; they were maintained in accordance with the institutional guidelines for animal welfare. Animals were deeply anaesthetized with ether and transcardially perfused with phosphate-buffered saline (PBS: 2.0 g NaH_2PO_4, 10.73 g Na_2HPO_4 and 9.0 g NaCl in 1,000 ml distilled water. pH 7.2) followed by perfusion with 4% paraformaldehyde. Brains were removed and immersed in the same fixative for several days. Serial coronal and horizontal sections (30 μm thick) were cut on a vibratome (VT1000E; Leica, Germany) and collected in 20% ethanol. For immunohistochemistry, we used affinity-purified antibodies directed against TRPC1 and TRPC5; these antibodies have been characterized in detail previously (Castellano et al. 2003; Facemire et al. 2004; Yuan et al. 2003). Sections were mounted onto gelatine-coated slides and incubated in affinity-purified antibodies against TRPC1 (rabbit antibody against the sequence QLYKDYTSKEQKDC residues 557–571; almone labs, Jerusalem, Israel; diluted 1:400), or against TRPC5 (rabbit antibody against

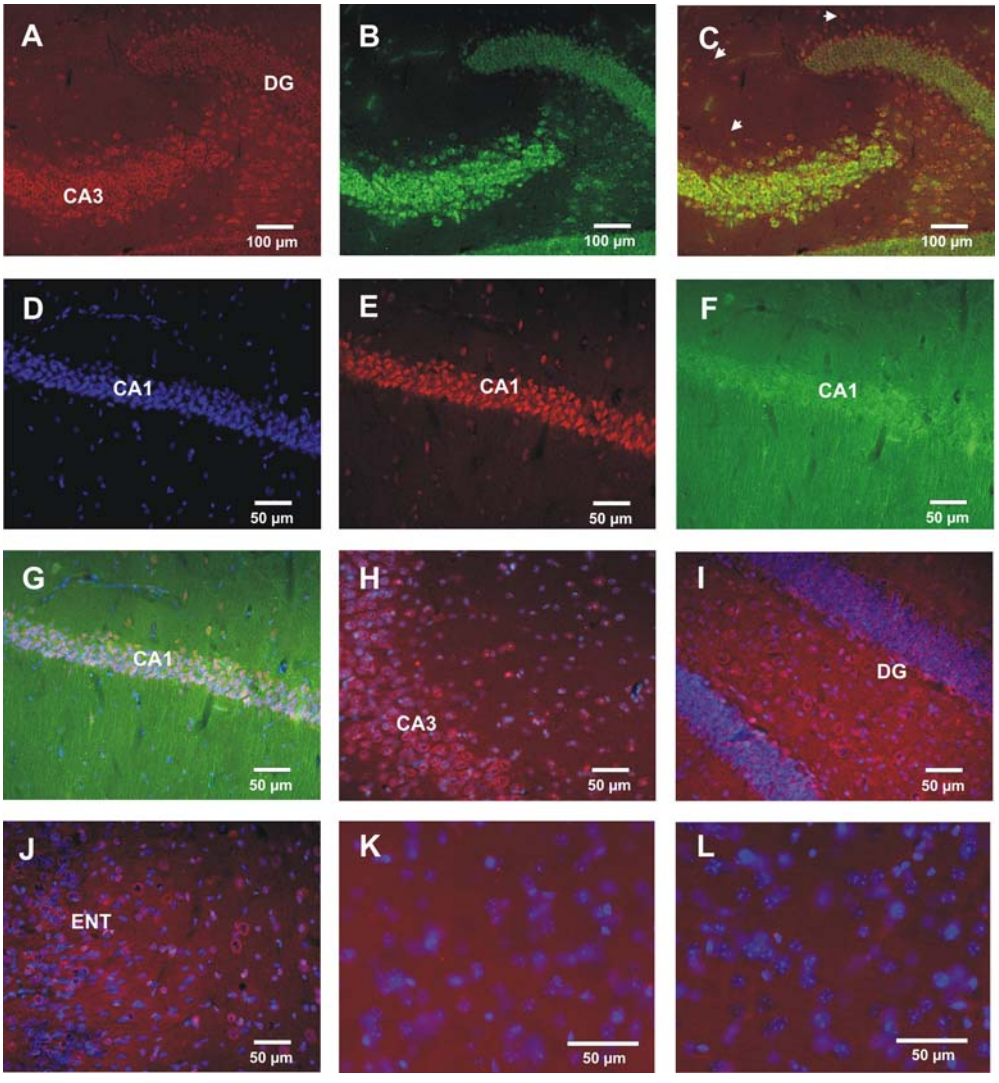

Fig. 2 Micrographs of anti-TRPC5-stained material and control experiments. **a** TRPC5 immunoreactivity (*red*) was mainly found on cell somata within the dentate gyrus (*DG*) and within area CA3 of the hippocampus. Horizontal section. **b** Same section as in **a**, but displaying NeuN immunoreactivity (*green*). **c** Overlay of **a**, **b** indicating co-localization of NeuN and TRPC5. However, several cells are TRPC5-positive, but not NeuN-positive (*arrows*), indicating that TPC5 can also be found on non-neuronal cells. **d** DAPI-stained cells (*blue*) in area CA1 of the hippcampus. Coronal section. **e** TRPC5 immunoreactivity (*red*) in area CA1 of the hippocampus (same section as in **d**). **f** Same section as in **d**, **e**, displaying MAP2 immunoreactivity. **g** Overlay of **d**–**f** indicating no co-localization of MAP2 and TRPC5. **h** Distribution of TRPC5-stained cells (*red*) in the area CA3 of the hippocampus. Horizontal section, counterstained with DAPI (*blue*). **i** TRPC5 immunoreactivity (*red*) in the dentate gyrus (*DG*). Note that not only cells in the granular layer, but also in the polymorph layer are immuno-positive for TRPC5. Horizontal section, counterstained with DAPI (blue). **j** TRPC5 immunoreactivity (*red*) in the entorhinal cortex (*ENT*) is not restricted to a specific layer but can be seen in the superficial and deeper layers. Horizontal section, counterstained with DAPI (*blue*). **k** Addition of the synthetic peptide with the sequence QLYKDYTSKEQKDC in excess blocks anti-TRPC1 staining. Counterstained with DAPI (*blue*). **l** Addition of the synthetic peptide with the sequence HKWGDGQEEQVTTRL in excess blocks anti-TRPC5 staining. Counterstained with DAPI (*blue*)

Table 1 Cell densities (mean± SEM) within the ROIs (representing an area of 10,000 μm^2) of the evaluated brain areas, for DAPI, TRPC1 and TRPC5 stained material (*LA* lateral nucleus of the amygdala, *BL* basolateral nucleus of the amygdala, *CE* central nucleus of the amygdala, *ME* medial nucleus of the amygdala, *CA1–CA3* areas of the hippocampus, *DG* dentate gyrus, *SUB* subiculum, *ENT* entorhinal cortex, *SEM* standard error of the mean)

Cells per 10,000 μm^2/brain area	DAPI-stained cells	TRPC1-positive cells	TRPC5-positive cells
LA	16.9±0.6	3.2±0.5	9.1±2.0
BL	13.2±0.5	3.4±0.4	6.3±0.6
CE	23.9±0.7	4.4±0.3	12.3±1.0
ME	21.8±0.8	2.4±0.5	12.2±1.4
CA1	31.1±1.6	4.5±0.4	22.2±1.9
CA2	24.5±1.8	6.5±0.8	19.3±1.1
CA3	24.1±1.3	5.6±0.7	15.3±1.7
DG	56.1±3.6	3.2±1.7	40.2±4.6
SUB	19.2±0.9	3.5±0.1	6.9±0.3
ENT	18.2±1.9	4.3±1.1	6.0±1.0

HKWGDGQEEQVTTRL almone labs; diluted 1:400) in the presence of 1% normal goat serum (NGS) and 0.3% TritonX-100 for 12 h at 4°C. After being rinsed, the sections were transferred to biotinylated anti-rabbit IgG (Vector, Burlingame, USA; diluted 1:200) for 2 h at room temperature, washed, incubated in Cy3-conjugated streptavidin (Jackson ImmunoResearch, West Grove, USA; diluted 1:2,000) for 2 h at room temperature, counterstained with 4,6-diamidino-2-phenylindole (DAPI; Molecular Probes, Leiden, Netherlands; diluted 1:15,000), washed and coverslipped in fluorescent mounting medium (DAKO, Carpinteria, USA).

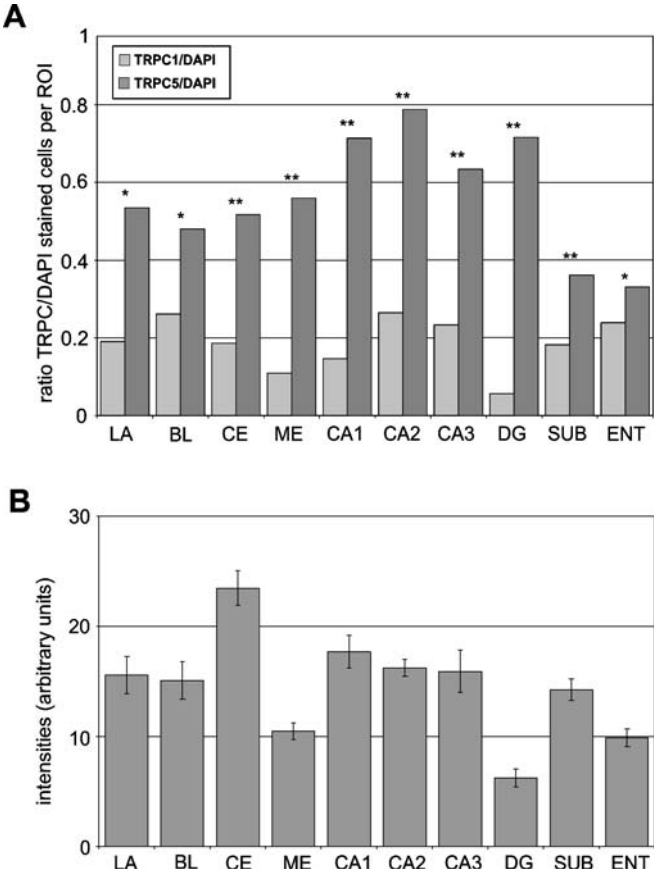

Fig. 3 Quantification of TRPC1 and TRPC5 staining in the amygdala, hippocampus and entorhinal cortex (*LA* lateral nucleus of the amygdala, *BL* basolateral nucleus of the amygdala, *CE* central nucleus of the amygdala, *ME* medial nucleus of the amygdala, *CA1–CA3* areas of the hippocampus, *DG* dentate gyrus, *SUB* subiculum, *ENT* entorhinal cortex). **a** Ratio of TRPC-stained/DAPI-stained cells per 10,000 μm^2 in the amygdala, hippocampus and entorhinal cortex (*P<0.05, **P<0.01; calculated with the unpaired *t*-test by comparing the values obtained from the calculation of the ratios of TRPC1/DAPI staining with the values obtained from the calculation of the ratios of TRPC5/DAPI staining). **b** Intensities of anti-TRPC1 immunostained material

Omission of the primary antibody gave no specific staining and specific staining was absent when antibodies were pre-incubated with control antigen peptides (both from almone labs; see Fig. 2k,l).

For the determination of whether neurons and/or non-neuronal cells expressed TRPC1 and TRPC5 channels, sections were immunostained with anti-NeuN antibodies (Chemicon, USA; diluted 1:100 in the presence of 0.1% TritonX-100 and 1% NGS) and the immunostaining was visualized with Cy2 (Jackson ImmunoResearch; diluted 1:1,500). After washing, sections were immunostained either for TRPC1 or for TRPC5. After further washes, sections were counterstained with DAPI, washed and coverslipped in fluorescent mounting medium (DAKO).

For the investigation of a possible dendritic localization of the channels, antibodies against MAP2 (Sigma, Deisenhofen, Germany) were used. After subsequent visualization with Cy2, the sections were immunostained for TRPC1 or for TRPC5, counterstained with DAPI and embedded.

An Axioplan 2 imaging microscope (Zeiss, Germany) with a computer-driven digital camera (Axiocam, Zeiss, Germany) and a 40× objective were used for analysis. For cell counts, regions of interest (ROI; representing a window of 10,000 μm^2) were delineated within the brain areas. Digital-image analysis-assisted manual counts of profiles were made by using ImageJ 2.19 (NIH, USA). Between three and six different ROIs were analysed per animal and brain region. The ratio of TRPC-stained and DAPI-stained cells was calculated for each brain area. For statistical evaluation, the unpaired *t*-test was performed with GraphPad Prism version 4.00 for Windows (GraphPad Software, USA).

Since TRPC1 was mainly found on dendrites rather than on the neuronal soma, intensity measurements were performed to compare the intensities of the staining in the different brain areas. For this purpose, ROIs of 10,000 μm^2

were defined and, within each region, the fluorescence intensities were measured by using ImageJ 2.19 (NIH); the colour-images were changed to 8-bit greyscale images that were represented by using unsigned integers in the range 0 to 255 (256 different grey values, coding for intensities). In each converted image, histograms of the distribution of pixel intensities were made and the mean value and the standard deviation were calculated (Kiprianova et al. 2004). The results were recorded in arbitrary units. For statistical evaluation, an analysis of variance (ANOVA), followed by the Newman-Keuls post-hoc test, was performed with GraphPad Prism version 4.00 for Windows (GraphPad Software).

Results

Immunoreactivity for both TRPC1 and TRPC5 channels was detected in all regions analysed (see below). Double-labelling with the TRPC antibodies and the antibodies directed against NeuN (a neuronal marker) revealed that TRPC1 was found on neurons, including both cell somata and dendritic trees (Fig. 1a–m). TRPC5 immunoreactivity was predominantly expressed by neurons, but also by non-neuronal cells (about 7%, Fig. 2a–c). TRPC5 staining was not found to overlap with dendritic MAP2 staining (Fig. 2d–g), indicating that TRPC5 was not localized on dendrites. Table 1 summarizes the densities of TRPC1-positive and TRPC5-positive cells.

Amygdala

The basolateral, lateral, central and medial nuclei of the amygdala were analysed. Immunoreactivity for both TRPC1 and TRPC5 was detected in each of these nuclei (Figs. 1a–b,d–f, 3a). However, TRPC5-labelled somata occurred more frequently than TRPC1-labelled cell bodies (Fig. 3a). In contrast to TRPC5, TRPC1 was mainly found on dendritic trees. Within the amygdala, the highest level of TRPC1 immunoreactivity mapped to the central nucleus (Fig. 3b).

Hippocampus and entorhinal cortex

The pyramidal layers of the areas CA1, CA2 and CA3 and the granular layer of the dentate gyrus were analysed within the hippocampal formation. In addition, the subiculum and the entorhinal cortex were studied. TRPC5-labelled somata were found in hippocampal areas CA1–CA3, in the dentate gyrus (Fig. 2a–i) and in the subiculum (Fig. 3a). In general, more TRPC5-labelled somata than TRPC1-labelled cell bodies were found in these areas, the strongest difference being found in the dentate gyrus (Fig. 3a). Likewise, a large number of TRPC5-positive somata were found within the entorhinal cortex (Fig. 2j).

As in case of the amygdala, high TRPC1 immunostaining was found on dendrites (Fig. 1c,g–m). The staining intensities were comparable with those seen in the lateral and basolateral nucleus of the amygdala, the only exception being the dentate gyrus, which showed a weaker signal (Fig. 3b, Table 2).

Table 2 Statistical analysis of TRPC1-staining intensities by using ANOVA, followed by the Newman-Keuls post-hoc test (*LA* lateral nucleus of the amygdala, *BL* basolateral nucleus of the amygdala, *CE* central nucleus of the amygdala, *ME* medial nucleus of the amygdala, *CA1–CA3* areas of the hippocampus, *DG* dentate gyrus, *SUB* subiculum, *ENT* entorhinal cortex)

ANOVA (Newman-Keuls multiple comparison test)	Q-value	*P*-value
DG vs. CE	12.63	0.001
DG vs. CA1	8.392	0.001
DG vs. CA2	6.542	0.01
DG vs. CA3	7.575	0.001
DG vs. LA	6.839	0.01
DG vs. BL	6.483	0.01
DG vs. SUB	5.869	0.01
ENT vs. CE	9.957	0.001
ENT vs. CA1	5.721	0.05
ME vs. CE	9.515	0.001
ME vs. CA1	5.28	0.05
SUB vs. CE	6.758	0.01
BL vs. CE	6.144	0.01
LA vs. CE	5.789	0.01
CA3 vs. CE	5.924	0.01
CA2 vs. CE	4.752	0.01
CA1 vs. CE	4.236	0.01

Discussion

The TRPC family is a structurally defined group of non-selective cation channels. PCR has detected mRNA for TRPC1 and TRPC5 in various brain areas in humans, including the amygdala and the hippocampus (Riccio et al. 2002). TRPC1 protein has been localized to the somata, axons and dendrites of primary cultures hippocampal neurons (Strubing et al. 2001). Furthermore, cultured hippocampal neurons from rat embryos at embryonic day 18 exhibit TRPC5-immunoreactive growth cones after 1–3 days in vitro; the signal is lost after 5–10 days in vitro (Greka et al. 2003). These channels are assumed to form heteromers, since in the hippocampus, TRPC1 and TRPC5 mRNA have overlapping distributions (Strubing et al. 2001). As shown by cell culture experiments on TRPC1- and/or TRPC5-transfected HEK293-M1 cells, the coexpression of TRPC1 and TRPC5 results in a novel non-selective cation channel, which is activated by G(q)-coupled receptors but not by depletion of intracellular Ca^{2+} stores (Strubing et al. 2001).

The finding that synaptosomes from adult rat brain do not consistently contain TRPC heteromeres (Goel et al. 2002) raises the question as to whether TRPCs exist in different cellular compartiments (Strubing et al. 2003).

TRPC1 has been mainly detected in the dendrites of neurons but can also be detected in neuronal cell bodies, whereas TRPC5 can be detected in the cell bodies of neurons and, to a lesser extent, of non-neuronal cells. Thus, functional heteromers of TRPC1 and TRPC5 may occur on the somata of some neurons. Concerning the dendritic localization, TRPC1 either forms heteromeric channel with an interaction partner other than TRPC5 or it forms homomeric channels. This latter view is supported by the notion that mixed TRPC heteromers are not present or are expressed only at undetectable levels in adult brain (Strubing et al. 2003).

In the hippocampus, TRPC5 channels have been shown to be involved in mechanism controlling neurite extension and growth cone morphology (Greka et al. 2003). Beyond this region, TRP channels seem to play a prominent role in neuronal signalling. Thus, metabotropic glutamate receptors have been linked to TRP channel activation in neurons of the CNS, suggesting an important role for these channels in synaptic communication via endogenous neurotransmitters (Tozzi et al. 2003; Kim et al. 2003; Bengtson et al. 2004; Gee et al. 2003). Moreover, muscarinic activation of a voltage-dependent cation non-selective current in the cortex has been described (Haj-Dahmane and Andrade 1996). Therefore, TRPC1 and TRPC5 channels in mammalian medial temporal lobe structures could play a prominent role in neuronal plasticity. However, this issue is still largely enigmatic.

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