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Chapter 2

TRP Channels in Neuronal and Glial Signal Transduction

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Additional information is available at the end of the chapter

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1. Introduction

Many physiological processes like muscle contraction, hormone secretion and intracellular signalling processes are triggered by calcium as intracellular signalling molecule. The signal transduction capacity of calcium depends on the 10,000-fold gradient across the plasma membrane with 2.5 mM extracellular and resting intracellular calcium ion concentration of approximately 100 nM. Low intracellular calcium concentrations are managed by the extrusion of calcium by ATPases and transporters [1, 2], whereas rapid and distinct increases in intracellular calcium up to micromolar concentrations are mediated by calcium-permeable ion channels of the plasma membrane as well intracellular calcium storage compartments. Calcium mediates its biological functions by protein structures capable to bind calcium. These calcium-binding domains are building blocks of the proteins modulated by calcium directly or part of calcium sensor proteins (calmodulin, calcium binding protein, calcineurin, S100, NCS etc) mediating calcium-dependent modulation by protein-protein interaction [3].

In excitable cells like neurons, heart or skeletal or smooth muscle cells, calcium currents first identified are mediated by voltage-gated calcium channels [4-6]. Later, additional calcium-permeable ion channels have been identified mediating hormone-induced calcium entry also in non-excitable cells like endothelial, epithelial, immune cells. The identity of these channels has been unravelled via analysis of phototransduction in flies [7]. Montell and Rubin cloned Transient Receptor Potential (TRP) from *Drosophila melanogaster* and described TRP as a phospholipase C-modulated, calcium-permeable ion channel [8]. Mammalian TRP-homologous channels have been identified by comparing the *Drosophila* TRP sequences with sequences resulting from the upcoming genome and expression profiling projects at that time. The first channel protein showing the highest degree of sequence similarities with *Drosophila* TRP were named classic TRP family (TRPC1) [9-11]. Additional TRP-homologous proteins establishing the melastatin-like and vanilloid-like TRP subfamilies, TRPM and TRPV, respectively, were identified by other approaches [12-14]. An additional fascinating feature of TRP channels

became obvious with the identification of TRPV1 (vanilloid receptor 1, VR1) as molecular target of capsaicin [15]. Capsaicin is the active molecule of chilli peppers and an irritant that is responsible for providing a sensation of burning, e.g., on the tongue. TRPV1 characterization revealed that TRP channels are targets of many secondary plant compounds and are involved in sensory functions [16]. Last but not least, the TRP superfamily comprises the mucolipin [TRPML [17]] and the polycystin [TRPP [18]] calcium-permeable channel proteins sharing a comparable transmembrane topology and features like ion permeability [13, 14, 19]. TRP channels are integrated in many cellular signal transduction pathways and a variety of physiological processes as discussed below.

TRP channels have been identified and characterized by common biochemical, immunochemical and physiological methods. The function of TRP channels can be directly studied by patch clamp electrophysiology as well as imaging techniques. Patch clamp techniques enable to monitor currents across the plasma membrane mediated by TRP channels using small electrodes in small pipettes together with the ground electrode in the bath solution [20]. In this configuration, the electrical activity of ion channels in the plasma membrane can be monitored. Depending on configuration and access of the electrode within the patch pipette, different configurations can be discriminated (cell-attached, whole cell, inside-out or outside-out). On the other hand, a growing number of methods has been developed to monitor changes in ion concentrations in intact cells using small chemical compounds or artificial proteins constructs [21]. Fura-2 is one of the best known calcium dyes, a small chemical compound changing its fluorescence features depending on calcium concentration [22]. In the meantime a variety of new compounds have been developed characterized by changed ion selectivity, changes in Kd values or fluorescence intensities. The intracellular concentration of the indicator dyes depend on the activity and capability of organic solute carrier to export the dyes and thereby lowering intracellular dye concentrations. This disadvantage can be overcome by the use of the new protein-based probes. These artificial proteins are constructs of ion binding domains conjugated with fluorescence protein domains transcribed transiently from transfected plasmids or permanently from genomic localized expression cassettes [23, 24].

The following review will give an introduction in the broad field of TRP channel research related to their expression in the central nervous system (CNS), their physiological function in neurons as well as in glia cells, and their role in neurological and psychiatric CNS disorders. The involvement of TRP channels in the pathophysiology of glioma and the sensing of pain is not discussed here [for comprehensive reviews please refer to [25, 26]].

2. TRP channels in the brain

2.1. TRPC channels

The classic TRP channel family comprises seven different genes with proteins showing the highest sequence similarity to the prototypic *Drosophila* TRP [8, 12, 19]. The mammalian channel proteins are involved in receptor-regulated calcium entry [27]. Receptor activation by hormones, neurotransmitter and in *Drosophila* light results in the phospholipase C-mediated

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breakdown of phosphatidylinositides leading to the formation of inositol 1,4,5-trisphosphate and diacylglycerol (Figure 1). Inositol 1,4,5-trisphosphate induces calcium release from intracellular stores via the activation of inositol 1,4,5-trisphosphate receptors (IP3 receptor), whereas diacylglycerol directly activates mammalian classic transient receptor potential (TRPC) channels (TRPC2, TRPC3, TRPC6 and TRPC7) in a protein kinase C-independent manner [27, 28]. The prerequisite of phospholipase C stimulation has been shown for TRPC1, TRPC4 and TRPC5 currents, however the molecular mechanism is still unclear [27].

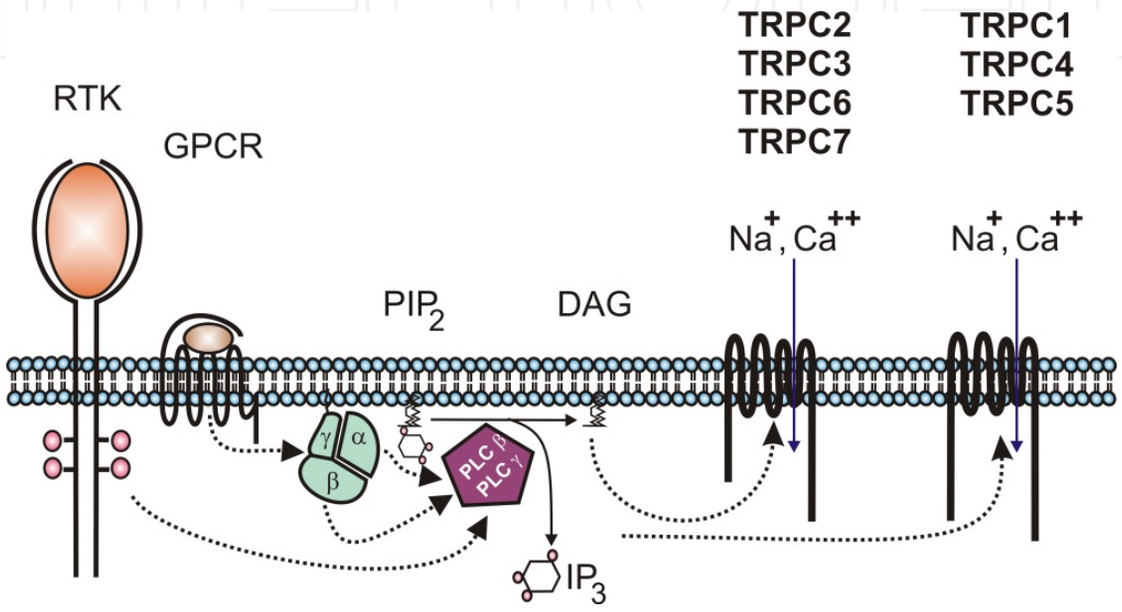

Figure 1. Receptor-induced activation mechanisms of TRP channels in mammals. RTK: receptor tyrosine kinase; GPCR: G protein-coupled receptor; PLC: phospholipase C; PIP2: phosphatidylinositol-4,5-bisphosphate; IP3: inositol-1,4,5-trisphosphate; DAG: diacylglycerol.

In the brain, TRPC1 expression was confirmed using a set of techniques ranging from RT-PCR, western blotting to confocal and electron microscopy. TRPC1 was detected in different brain regions of adult mice including the cerebellum, the hippocampus, the basal ganglia, the amygdala and the forebrain [29-31]. Strübing et al. showed that TRPC1 and TRPC5 channels are expressed in similar brain areas suggesting that they might form heteromers for example in the hippocampus [31]. However, empirical evidence for the existence of these heteromers is still lacking [32]. Only little is known about the distribution of TRPC channels in neurons. TRPC5 channels were suggested to be expressed mainly in distal dendrites and dendritic spines in lateral septal neurons. However, the expression pattern might differ in different brain areas and neurons [33]. Interestingly, TRPC1 protein was not only detected in neurons such as in the hippocampal CA1 or CA3 pyramidal cells [31], but also in astrocytes and oligodendrocyte progenitor cells [34-36]. Furthermore, mRNA for all TRPC channels including TRPC1 was found in the cortex of the mouse developing brain [37]. TRPC1, together with TRPC3 and TRPC5 were the main isoforms detected in this study. This expression pattern might be time dependent and species specific because TRPC4 and TRPC5 were the most prominent isoforms in the adult rat prefrontal cortex [38], whereas TRPC3 and TRPC6 channels are major TRPC

mRNAs detected in adult mice [29]. TRPC2 being expressed in the rodent vomeronasal organ is clearly an exception [39]. In humans, TRPC2 is a pseudogene; the transcribed mRNA is functionless due to various stop codons [40]. In rodents, the transcription of the TRPC2 gene results in a functionally active protein involved in sensory responses to pheromones [39]. Genetic inactivation of TRPC2 in mice leads to loss of sex discrimination of male mice [41-43]. TRPC4 mRNA expression was observed in the adult mouse brain in the cortex, the hippocampus, the thalamus, the amygdala, the basal ganglia as well as the prefrontal cortex [29, 30, 38, 44]. TRPC4 protein expression was shown in the hippocampus, the cortex as well as the cerebellum [38, 44]. Using in situ hybridisation or immunocytochemistry, the expression of TRPC4 channels in different brain areas was specified. For example, TRPC4 was detected in cell layers of the prefrontal cortex [38] or in pyramidal CA1 and CA3 neurons of the hippocampus. In lateral septal neurons, TRPC4 channels were found on the cell surface of the soma and primary dendrites [33].

TRPC3 and TRPC6 mRNAs were demonstrated in the basal ganglia, the cerebellum, hippocampus as well as the forebrain [29]. TRPC3 protein expression in the brain especially in the prefrontal cortex and cerebellum was not only shown in rat and mouse tissues but also in human tissue obtained from subjects of different age groups [45]. TRPC3 channel expression was higher in the developing cortex compared to the adult cortex, whereas TRPC3 cerebral expression was not age-dependent. The protein expression of TRPC6 channels in the hippocampus is controversial. While several groups using pharmacological approaches or RT-PCR or western blot analyses describe TRPC6 channels being expressed in all hippocampal regions [46-51], Nagy and co-workers as well as Chung and colleagues show expression of TRPC6 channels selectively in the dentate gyrus and interneurons [52, 53]. Interestingly, in contrast to Tai et al. 2008, who described TRPC6 expression in hippocampal CA1 soma as well as in dendrites, Nagy's data suggest that TRPC6 channels are mainly expressed in dendrites of interneurons and neurons from the dentate gyrus [49, 53]. In the developing brain TRPC6 channels protein expression peaked between postnatal day 7 and 14, a period known to be important for maximal dendritic growth [49]. For TRPC7, only low mRNA expression levels were published [29, 30]. TRPC3 channels are also expressed in astrocytes [54].

2.2. TRPM channels

Melastatin, the founding member of the melastatin-like TRP family, was identified within a screen for proteins differentially regulated in melanocytes and melanoma cells [55]. Analysis of clinical data showed that the presence of melastatin expression in melanoma patients inversely correlates with the severity and survival [56-58]. Although melastatin is the first member of the TRPM family its activation mechanism and physiological role is still unclear. In line with the first description as protein involved in melanocyte physiology several reports confirmed this view. A completely unexpected function, the integration in retinal signal processing, has recently been discovered by the identification of TRPM1 expression in retinal ON bipolar cells [59]. The critical role of TRPM1 in mammalian phototransduction is also highlighted by several reports describing TRPM1 mutations in patients suffering from congenital stationary night blindness [60-63]. Only very little is known about TRPM1 function

and expression in the CNS. Rather low mRNA TRPM1 expression was found in three studies in the brain [29, 64, 65].

From sequence similarity, TRPM3 is phylogenetically the closest neighbour to melastatin. TRPM3 is a polymodal ion channel activated by a variety of different stimuli like hypotonicity [66], sphingolipids [67], steroids [68, 69], nifedipine [69], and heat [70]. TRPM3 is activated by hypotonic extracellular solution and represents together with TRPV4, the volume-regulated TRP channels in the kidney [71, 72]. With the help of pharmacological tools, calcium entry induced by the application of hypotonic extracellular solutions can be assigned to TRPV4 and TRPM3 [71, 73-75]. While TRPV4 is activated by 4α-Isomers of phorbolesters and is blocked by ruthenium red, TRPM3 is activated by sphingosine and by pregnenolone-sulphate and blocked by gadolinium ions. TRPM3 is expressed in different areas of the CNS such as the hippocampus, the corpus callosum, the cortex or the hippocampus. These findings were reproduced in different studies using RT-PCR [29], northern blot [66, 76], as well as immunohistochemistry [77, 78]. TRPM3 channels are found in neurons (cerebral Purkinje neurons) as well as in oligodendrocytes [76-78]. Interestingly, neuronal expression of TRPM3 is present throughout development. However, it is almost lost in the adult brain [77]. In contrast, TRPM3 is highly expressed in oligodendrocytes in the adult brain.

The phylogenetically next neighbours to TRPM1 and TRPM3 are TRPM6 and TRPM7 [79]. The latter ones are involved in the body magnesium homeostasis [80]. While TRPM7 is ubiquitously expressed, TRPM6 is expressed in epithelial cells of the gut and the kidney and responsible for magnesium absorption and reabsorption. Loss-of-function mutations in TRPM6 are linked to autosomal-recessive hypomagnesemia with secondary hypocalcemia [81, 82]. TRPM6, TRPM7 and TRPM2 share a common structural feature. All three genes code for chimeric proteins combining a hexahelical transmembrane channel forming domain with a C-terminal enzymatic active domain [83]. In the case of TRPM6 and TRPM7, the pore-forming domains are fused to atypical alpha kinase-like structures. The functional role for the enzymatic domain is still under dispute. TRPM6 and TRPM7 are permeable for magnesium and for other essential divalent cations like Ca^{2+}, Zn^{2+}, Mn^{2+}, Co^{2+} as well as toxic cations like Ba^{2+}, Sr^{2+}, Ni^{2+}, Cd^{2+} [84, 85]. While TRPM6 mRNA was detected at low level in different brain areas [29], nothing is known about its role in the CNS. In contrast to TRPM6 channels, TRPM7 mRNA is highly expressed in the brain [29, 86]. In primary hippocampal neurons as well as in pyramidal hippocampal CA1 neurons in rat brain slices, TRPM7 was detected by different groups using immunocyto- and immunohistochemistry [87-89].

While divalent ions are the preferentially carried ion of TRPM6- and TRPM7-mediated currents, TRPM4 and TRPM5 form ion pores impermeable for divalent ions and allow selectively sodium to pass [90]. As sodium channels, TRPM4 and TRPM5 are paradoxically activated by increased intracellular calcium concentrations and represent calcium-activated sodium channels. TRPM4 is expressed in different brain regions including the thalamus, the hypothalamus, the medulla oblongata, the hippocampus and the spinal cord in mouse, rat as well as human brain (Lein et al., 2007; [29, 91]. In contrast to TRPM4, the expression of TRPM5 is restricted to a few cell types. TRPM5 is expressed in taste buds of the tongue and involved in the sensation of bitter and sweet taste [92, 93].

The remaining two TRPM channels proteins, TRPM2 and TRPM8, can also be discussed in the light of sensory functions. As already mentioned, TRPM2 represents a chimeric protein integrating an ADP-ribose hydrolase domain C-terminal to the pore-forming transmembrane domains [83]. Simultaneously to the ADP-ribose hydrolysing activity of the C-terminal enzymatic domain, TRPM2 is activated by ADP-ribose and it has been shown that the C-terminal part is essential for the function of the pore forming channel protein [94, 95]. Increased intracellular ADP-ribose concentrations are linked to genotoxic and/or oxidative stress of cells leading to the activation of the poly(ADP-ribose) polymerase (PARP) modulating protein stability by the mono and poly ADP-ribosylation of proteins [96]. This process of protein stability regulation is additionally controlled by an enzyme called poly(ADP-ribose) glucohydrolase (PARG). PARG reduces the post-translational poly ADP-ribose modifications to mono ADP-ribosylation, thereby increasing the intracellular ADP-ribose concentration leading to the activation of TRPM2. In whole cell calcium imaging experiments, the extracellular application of hydrogen peroxide results in the activation of TRPM2 validating its function as redox sensor. TRPM2 channels are preferentially expressed in microglia cells, the host macrophages of the CNS [97, 98]. In addition, in several brain regions such as the hippocampus, the cortex and the substantia nigra TRPM2 channels were also detected in neurons using RT-PCR, western blotting as well as immunohistochemistry [99, 100]. It was suggested that TRPM2 and TRPM7 channels form heteromers because knock-down of TRPM7 with siRNA is accompanied by down-regulation of TRPM2 channels [101]. TRPM8, the cold sensor, is mainly expressed in sensory neurons. TRPM8 is activated at temperatures between 8 °C to 28 °C as well as the secondary plant compound menthol and synthetic cooling compounds. Together with TRPA1, TRPM8 represent the cold sensors in human. Noxious cold is mediated by TRPA1 [26, 102].

2.3. TRP channels in the brain - TRPV channels

Vanilloid structures, derivates of vanillin comprising eugenol, zingerone and capsaicin, are found in many spice plants and known for their individual characteristic flavour. Beside the use as spice, vanilloid containing plant extracts are used as remedy in the various traditions of folk medicines. Therapeutic and experimental use of capsaicin in pain treatment inspired research resulting in the unravelling of the molecular target of capsaicin. The molecular target, an ion channel related to *Drosophila* TRP, was named capsaicin or vanilloid receptor and became eponym of the subgroup or structurally related ion channels of the TRP channel superfamily [15]. The vanilloid-like TRP channels comprise six members, four proteins (TRPV1 to TRPV4) like TRPV1 are non selective ion channels involved in thermosensation [14, 73, 74, 102, 103], while two ion channels (TRPV5 and TRPV6) represent highly calcium-selective ion channels [75, 104].

The warm and heat sensors (TRPV1 to TRPV4) and the cold sensors (TRPM8 and TRPA1) represent the thermosensors of the human body and cover the complete temperature range necessary for human life. As warning sensors expressed in dorsal root ganglia, the thermo TRPs are also involved in sensation and modulation of pain and therefore interesting as molecular targets for new pain-treating drugs. Most studies dealing with the structural and

functional properties of the TRPV channel family in the CNS are focused on TRPV1. However, TRPV2, TRPV3 and TRPV4 are also detected in the CNS. In contrast for TRPV5 and TRPV6, there is no evidence for their expression in the CNS.

Localization	Function	References
Hippocampus (interneurons, dentate gyrus)	involved in anxiety and fear	[132, 151]
	involved in LTD	[152, 153]
	involved in LTP	[152]
	involved in pathogenesis of epilepsy	[126, 127]
hypothalamus	central osmoregulation	[154, 155]
	central regulation of temperature	[108]
Locus coeruleus	potentiation of glutamate,	
	adrenaline or norepinephrine release	[151]
Cortex	involved in cortical excitability	[156]
	involved in pathogenesis of epilepsy	[126]
Striatum	facilitation of glutamatergic	[157]
	postsynaptic neurotransmission	[158]
	glutamate release	[159]

Table 1 Localization and putative function of TRPV1 channels

TRPV1 expression in the CNS was investigated using a variety of methods ranging from pharmacological characterization and immunohistochemistry [105] to RT-PCR [106], western blotting to radio ligand binding [107]. Beside the great variety of methods and studies the expression of TRPV1 in the brain remains controversial. Several studies showed a wide spread TRPV1 expression in the CNS suggesting an expression of TRPV1 in pyramidal neurons of the CA1, CA3 area of the hippocampus, the dentate gyrus, the locus coeruleus, the hypothalamus, the substantia nigra, the cerebellum, the cortex and other limbic structures [108]. Other studies reported TRPV1 expression which was highly restricted to primary sensory ganglia with minimal expression in few brain regions which are adjacent to the caudal hypothalamus [107] (expression profiles and methods are summarized in Table 1). However several groups used TRPV1 agonists or antagonists as well as TRPV1 knock-out mice to define the role of TRPV1 channels in the CNS and reported versatile functions in different brain regions such as the hippocampus, the substantia nigra, the cortex or the hypothalamus. TRPV1 channels are not only activated by capsaicin but also by the CB1 agonist anandamide [109], other endovanilloids such as N-acyldopamines or the endogenous lipoxygenase derivates HPETE which are released for example in the hippocampus after mGluR1 activation [108]. Importantly, colocalization of TRPV1 and CB1 receptors was found in different mouse brain regions including

the pyramidal cells of the hippocampus and basal glia [110, 111]. Regarding its cellular localisation, TRPV1 channels were detected in neuronal cell bodies, presynaptic terminals as well as in dendrites on postsynaptic spines [105, 106, 112, 113]. Furthermore, these channels are also present in pericytes and at the feet of astrocytes surrounding small vessels [105, 114].

TRPV2 channels are widely distributed in the brain compromising the colocalisation with TRPV1 in the cortex [19, 112, 115, 116]. TRPV3 mRNA was detected throughout the cortex, hippocampus, thalamus, striatum and cerebellum [117, 118]. TRPV4 mRNA is present in the hypothalamus, the cerebellum, basal ganglia, as well as in pyramidal neurons of the hippocampus [29, 119, 120]. Importantly, TRPV1-4 were also found in astrocytes [121, 122].

3. TRP channels in CNS diseases

3.1. Developmental disorders — Rett syndrome

Rett syndrome (RTT) is severe X-linked neurodevelopmental disorder which is unique among genetic, chromosomal and other developmental disorders because of its extreme female gender bias, early normal development, and subsequent developmental regression with loss of motor and language skills. RTT is caused by heterozygosity for mutations in the X-linked gene *MECP2*, which encodes methyl-CpG binding protein 2. Rett syndrome patients suffer from stereotypic wringing hand movements, social withdrawal, communication dysfunction, cognitive impairment, respiratory dysfunction as well as failing locomotion [123]. MeCP2 regulates expression of multiple genes, including BDNF. BDNF signaling was strongly altered in Mecp2 mutant mice [48].

Importantly, TRPC3 and TRPC6 channel expression and function was significantly lower in the hippocampus and several other brain regions of Mecp2 mutant mice revealing a cellular phenotype certainly contributing to hippocampal dysfunction in Mecp2 mutant mice as well as Rett syndrome etiology. These results suggest that compounds which enhance BDNF release or boost TRPC3/TRPC6 channel function might be an interesting new preclinical concept which needs to be evaluated in Rett mouse models [124, 125].

3.2. Epilepsy

Recent data suggests that TRPV1 channels might contribute to the pathophysiology of epilepsy. In the cortex and hippocampus from patients suffering from mesial temporal lobe epilepsy, the most common form of chronic and intractable epilepsy, TRPV1 mRNA and protein expression was significantly increased compared to healthy controls [126]. In a mouse model of temperal lobe epilepsy, these findings were supported [127]. The expression of TRPV1 in the dentate gyrus was significantly enhanced. Furthermore, capsaicin and anandamide significantly enhanced glutamate release in a TRPV1-dependent manner in mice with temperal lobe epilepsy [128, 129]. In contrast, the TRPV1 antagonist capsazepine reduced 4-aminopyridine-induced seizure-like activity in mice [128].

Beside TRPV1 channels, data from knockout mice point to a role of TRPC1/4/5 as well as for TRPC3/6 channels in the pathophysiology of epilepsy. Phelan et al. described a major role of TRPC1 and TRPC4 channels in the plateau potential of lateral septal neurons which show a high vulnerability to seizure-induced neuronal death as well as direct excitotoxicity by the application of group I mGluR receptor agonists [33]. *In vivo* results using the pilocarpine-induced status epileptics in TRPC1/TRPC4 double knockout animals showed surprising results. Cell death was significantly reduced in the lateral septum but also in the CA1 region of the hippocampus after severe seizures. However, the severity of the seizures *per se* was not altered. The authors concluded that this conundrum might be explained by the hypothesis that TRPC5 channels might be important for epileptiform burst in other limbic brain areas. This hypothesis was recently supported using TRPC5 knockout mice [32]. They exhibit significantly reduced seizures and minimal seizure-induced cell death in the CA1 region of the hippocampus. Importantly, spatial learning was not affected making TRPC5 channels an attractive novel target for the treatment of epilepsy.

TRPC3 channels are also discussed to play a "toxic" role in status epilepticus [46, 130]. After pilocarpine-induced status epilepticus in rats, TRPC3 expression was significantly enhanced in CA1, CA3 pyramidal neurons as well as dentate granule cells, whereas TRPC6 channel expression was reduced in these areas. Using two pharmacological approaches, first the inhibition of TRPC3 with the selective antagonist Pyr3 and second activation of TRPC6 channels with the TRPC6 activator hyperforin protected against neuronal damages following the status epilepticus [46].

3.3. Migraine

TRP channels might be involved in several processes relevant for the pathophysiology of migraine such as altered central calcium homeostasis, multimodal sensory and pain perception, or central or peripheral sensitization. Therefore, a recent study investigated single nucleotide polymorphisms (SNPs) in TRP genes in 1040 patients and 1037 healthy controls in Spain. For TRPV1, a nominal association was found for TRPV1 rs 222741 in the overall migraine group, for TRPV3 a correlation with TRPV3 rs7217270 was detected in the migraine group with aura [131].

3.4. Mood disorders – anxiety, unipolar and bipolar depression

TRPV1 and TRPV3 channels might be involved in fear and anxiety [107, 132]. TRPV1 knockout mice showed decreased anxiety-related behavior in several behavior paradigms such as the elevated plus maze test or the light dark test [107, 132]. Furthermore, fear and stress reaction were also reduced in TRPV1 knockout mice [107]. Therefore, TRPV1 antagonists such as capsazepine were investigated when they were applied directly into the ventral hippocampus or the periaqueductal grey. In both studies capsazepine showed anxiolytic effects. Recent studies investigated if compounds which act on both TRPV1 as well as CB1 receptors might be more effective than selective TRPV1 blocker [133]. N-arachidonoyl-serotonin which blocks TRPV1 channels and indirectly activates CB1 receptors and Arachidonyl-2-chloroethylamide (ACEA) which activates both TRPV1 as well as CB1 receptors were investigated. N-arachi-

donyl-serotonin was more effective than arachidonyl-2-chloroethylamide in behavioral paradigms for anxiety [134, 135]. The TRPV1/CB1 agonist ACEA showed anxiolytic effects in a bell shaped dose dependency in a mouse model using electrical stimulation of a brain area, the medial dorsal periaqueductal gray, which has an important role in orchestrating anxiety- and panic-related responses [133, 136]. The panicolytic effects are dependent on CB1 receptors. Importantly, in higher concentrations ACEA loses its anxiolytic effect probably via TRPC1 activation. This assumption is supported by the finding that ACEA effects in higher concentrations can be unmasked by the addition of the TRPV1 antagonist capsazepine. TRPV1 blockade per se also showed panicolytic effects suggesting opposite functions for TRPV1 and CB_1 receptors in the modulation of panic-like responses [136].

The evidence for the role of TRPC6 channels in depression comes from the active antidepressant constituent of St. Johns wort, hyperforin. Hyperforin resembles in its effects several classical antidepressants and neurotrophic factors such brain derived neurotrophic factor (BDNF) or nerve growth factor (NGF) [137-140]. Hyperforin inhibits neurotransmitter reuptake and improves synaptic plasticity ranging from increased neuritic outgrowth in PC12 cells to altered spine morphology in CA1 and CA3 neurons of the hippocampus via the activation of TRPC6 channels [137-139]. Recently, we showed that several signal cascades are involved in the alteration of synaptic plasticity such as Ras/MEK/ERK, PI3K/Akt as well as CAMKIV which finally result in CREB phorsphorylation [137]. In addition, enhanced CREB phosphorylation and TRPC6 channel expression was detected in the cortex but not the hippocampus after chronic hyperforin treatment for 4 weeks in adult mice [141]. However, hippocampal neurogenesis remained unchanged. Bouron et al. suggests that not only the hyperforin-mediated calcium influx but also its effects on intracellular zinc might be important for its antidepressant activity [142, 143]

Oxidative stress, mitochondrial dysfunction, and disrupted intracellular Ca^{2+} homeostasis are discussed to play a role in bipolar disorder (BD). TRPM2 channels, as a regulator and connector between reactive oxygen species (ROS) and intracellular Ca^{2+}, seem to be implicated in bipolar disorder. In B-lymphocytes from patients, TRPM2 channel expression is elevated associated with enhanced intracellular Ca^{2+} levels [144]. In addition, several groups reported genetic association between several intronic and extronic single nucleotide polymorphisms in TRPM2 and BD [145-149]. In a recent study using B-lymphocytes from small group of patients (n = 6) suffering from bipolar disorder, no change in TRPM2 expression could be detected. However, they were more susceptible to oxidative stress when stimulated with H_2O_2 [150].

3.5. Multiple sclerosis

Multiple sclerosis is a neurodegenerative disease caused by chronic inflammation of the CNS. Schattling et al. recently demonstrated that TRPM4 channels are involved in the pathogenesis of multiple sclerosis by using TRPM4 knockout mice and inducing an experimental autoimmune encephalomyelitis (EAE) in these animals [91]. TRPM4 channels are located in hippocampal neurons from mice and humans as well as in the spinal cord and cortex. TRPM4 deficiency reduced overall disease severity. Importantly, deficiency or pharmacological inhibition of TRPM4 resulted in reduced axonal and neuronal degeneration without altering

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EAE relevant immune function. In addition, axonal TRPM4 expression in axons was significantly elevated in demyelinating white matter brain lesions of patients with multiple sclerosis in comparison to healthy controls. The authors further demonstrate that TRPV4 channels are involved in toxic effects of high glutamate levels which are a major contributor to neurodegeneration in multiple sclerosis.

4. Conclusion

Transient receptor potential (TRP) channels comprise a large family of non selective, calcium-permeable channel proteins which are activated and regulated by different mechanisms. TRP channels respond to secondary plant compounds as well as intracellular stimuli such as calcium, metabolites of the arachidonic acid or phosphatidylinositol signal transduction pathways. TRP channels sense environmental stimuli such as changes in temperature, osmolarity and pH and represent the molecular target of pheromones, taste and secondary plant compounds. The broad function of TRP channels in CNS physiology becomes apparent through their involvement in several psychiatric and neurological CNS disorders. This makes them an interesting topic for further research and drug development. The diversity of the chemical structures and the selectivity of the naturally occurring compounds modulating TRP channels show the possibility for pharmacological modulation of TRP channels and inspire the development of new synthetic structures for TRP channel interference at bench and bedside.

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