# Physiological Roles of TRPM4

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Transient receptor potential melastatin 4 (TRPM4) is a unique member of the TRPM protein family and, similarly to TRPM5, is Ca2+ sensitive and permeable for monovalent but not divalent cations. It is widely expressed in many organs and is involved in several functions; it regulates membrane potential and Ca2+ homeostasis in both excitable and non-excitable cells.

Physiological TRPM4 Endocrine Pancreas Vascular heart

## 1. Presence of TRPM4 in Various Cells/Organs

Even before the discovery of TRPM4, which is the ion channel responsible for the calcium-activated monovalent cation currents, several reports suggested a role for these currents, for instance in neonatal rat cardiac cells [1] and outer hair cells of guinea pig cochlea [2]. Since that time, TRPM4 expression has been confirmed in several tissues and cell types and a potential role for TRPM4 has been suggested. The smooth muscle cells [3] of the vasculature [4][5][6], the urinary bladder [7][8][9][10], and the colon [11]; the endothelium [12][13]; immune cells [14][15]; several parts of the central nervous system [16]; endocrine cells of the islets of Langerhans [17][18]; adipocytes [19]; keratinocytes [20]; mucin secreting cells [21]; human valve interstitial cells [22]; and skeletal muscle [23] all express TRPM4. TRPM4 was implicated in various types of cancer [24][25]. TRPM4 expression is also pronounced in the heart and the channel can contribute to the function of various types of cardiac cells including sinoatrial nodal cells [26][27], atrioventricular nodal cells [28], cells of the conduction system [29][30], and atrial [31][32] and ventricular myocytes [33][34].

## 2. Physiological Importance of TRPM4

### 2.1. The Role of TRPM4 in the Secretory Mechanism of the Endocrine Pancreas

TRPM4 can be involved in the function of islets of Langerhans [17]. A $Ca^{2+}$-activated non-specific cationic current ($I(NSC_{Ca})$) was described before the discovery of TRPM4. A current inhibited by adenosine triphosphate (ATP) was described in CRI-G1 rat insulinoma cells [35] and in β-cells of human and murine islets [36]. As phosphatidylinositol 4,5-bisphosphate (PIP2) effectively facilitates the activation of TRPM4 and the PIP2 level increases upon the activation of β-cells by glucose, it is tempting to speculate that TRPM4 is indeed important to the function of these cells. Furthermore, as β-cells are the targets of the antidiabetic drug glibenclamide, and it was shown that glibenclamide inhibits TRPM4, this also suggests a role for TRPM4. Indeed, TRPM4 RNA is present in several β-cell lines such as HIT-T15 (hamster), RINm5F (rat), β-TC3, and MIN-6 (mouse) [37]. Not only was the presence of TRPM4 mRNA confirmed, but a TRPM4 protein was also shown in RINm5F and in INS-1 rat β-cell lines [38] and in

human pancreatic islets [37]. In these cell lines, the glucose- and arginine vasopressin-induced stimulation led to depolarization and insulin secretion with two phases. The first phase was due to the activation of the TRPM4 channels and the second, slower phase was due to the recruitment of TRPM4-containing vesicles to the plasma membrane [38]. In cells expressing the dominant negative TRPM4 construct, depolarization and insulin secretion were much smaller. Similarly, two phases of depolarization and insulin secretion were induced in the β-cells of other species in response to various stimuli, including glibenclamide on top of glucose and arginine vasopressin [37]. Not only was the dominant negative construct effective in reducing the stimulation-induced insulin secretion, but 20 and 30 µM 9-phenanthrol also reduced insulin secretion induced by glucose and GLP-1 in isolated rat islets [39]. Similarly, GLP-1-induced insulin secretion—mediated by Protein Kinase C (PKC) and the mobilization of intracellular $Ca^{2+}$ from thapsigargin-sensitive $Ca^{2+}$ stores—involved TRPM4 activation, as it was negligible in the TRPM4 knock-out (KO) mice [40]. Pancreatic α-cells (α-TC1-6 murine cells) also express TRPM4 both at the RNA and protein levels, and TRPM4 contributes to agonist-induced depolarization and glucagon secretion as TRPM4 knockdown significantly reduced both depolarization and glucagon secretion upon stimulation with arginine vasopressin, KCl, L-arginine, and BayK 8644 [41]. Similarly, the hamster α-cell line INR1G9 also functionally expressed TRPM4, but, unlike in β-cells, no second phase was observed [37]. Although several studies indicate that TRPM4 has a role in insulin secretion, it must be noted that TRPM4 KO animals do not have hyperglycemia, insulin deficiency, or diabetes mellitus, so further studies are required to elucidate the physiological role of TRPM4 in the function of the endocrine pancreas.

## 2.2. The Role of TRPM4 in the Immune System

TRPM4 was also connected to the function of various immune cells. Although the presence of TRPM4 RNA was not detected in human spleen, thymus, or lymphocytes [42]; TRPM4 protein was present in mouse thymocytes, in D10.G4 cells (murine Th2 cell clone), in Molt-4, and Jurkat cells (human T lymphoblast cell lines) [15]. TRPM4 might play a negative feedback role in the activation of immune cells as an expression of the dominant negative TRPM4 construct, and the small-interfering RNA (siRNA)-mediated TRPM4 silencing converted the phytohemagglutinin-induced intracellular $Ca^{2+}$ oscillations to a sustained $Ca^{2+}$ concentration increase. Reduction of TRPM4 currents led to an increase in IL-2 production [15]. TRPM4 activation would lead to depolarization, which, by reducing the driving force for $Ca^{2+}$ entry and acting in concert with other channels, can control $Ca^{2+}$ oscillations in lymphocytes. A similar negative feedback role for TRPM4 was suggested in stimulated mast cells [14]. $Ca^{2+}$ signals, the release of histamine, leukotrienes, and tumor necrosis factor, as well as IgE-mediated cutaneous acute—but not chronic—phase allergic reactions, were all augmented in TRPM4 KO mice [14]. TRPM4 contributed to the migration but not to the maturation of murine dendritic cells by different mechanisms [43]. Migration of bone-marrow-derived mast cells was also reduced in TRPM4 KO mice [44]. TRPM4 expression was higher in murine Th2 cells compared with Th1 ones and differentially regulated $Ca^{2+}$ signaling and the nuclear factor of activated T-cells (NFATc1) localization [45]. The reduction of TRPM4 expression by siRNA led to an increased $Ca^{2+}$ influx and oscillatory levels in Th2 cells but the opposite effect was observed in Th1 cells. Furthermore, TRPM4 silencing reduced cell velocity and motility in Th2 cells but increased these functions in Th1 cells [45]. TRPM4 function improved survival in a murine sepsis model by facilitating monocyte and macrophage, but not neutrophil, functions including AKT signaling pathway-mediated phagocytic activity [46]. The compound 9-phenanthrol induced the degranulation of mast cells in vitro,

although not due to TRPM4 inhibition, but likely by activating type 3.1 $Ca^{2+}$-activated $K^+$ channels [47]. Nevertheless, 9-phenanthrol used in combination with imiquimod in a murine tumor model enhanced the in vivo degranulation of mast cells, the migration of dendritic cells, and the expansion of antigen-specific cytotoxic T lymphocytes thereby improving the efficiency of prophylactic immunization [47]. TRPM4 is involved in the function of several types of immune cells, at least in mice. TRPM4′s mRNA level was smaller in peripheral blood-derived mononuclear cells of patients suffering from psoriasis than in cells from healthy subjects, indicating the possible role of TRPM4 in the pathogenesis of psoriasis [48]. A recent article described TRPM4 as the target of protein arginine methyltransferase 5-mediated alternative splicing in activated murine T cells [49].

## 2.3. The Role of TRPM4 in the Regulation of Vascular Tone

TRPM4 has been extensively studied in vascular smooth muscles. One report mentioned a current activated by noradrenalin having permeability for monovalent cations in smooth muscle cells of rabbit ear arteries [50]. TRPM4 RNA was shown in whole rat cerebral arteries, in smooth muscle cells isolated from those vessels [51], and also in rat aorta and pulmonary vessels [52]. Smooth muscle cells isolated from cerebral arteries express the TRPM4 protein [53][54]. In rat cerebral arteries, TRPM4 mediated pressure-induced myogenic vasoconstriction [51] in a PKC-regulated manner [55]. Additionally, basal PKCδ activity increased the cell surface expression of TRPM4, thereby enabling TRPM4-mediated vasoconstriction [53][56]. In these studies, TRPM4 antisense oligodeoxynucleotides applied with reverse permeabilization technique on isolated arteries proved the role of TRPM4. The use of TRPM4 antisense oligodeoxynucleotides confirmed the role of TRPM4 in in vivo tests, as the suppression of TRPM4 led to decreased cerebral artery myogenic constrictions and impaired autoregulation [57]. In rat cerebral arterial myocytes, TRPM4 could contribute to membrane stretch-induced depolarization [58]; although the direct stretch sensitivity of TRPM4 was not confirmed, and it is likely that such a stretch leads to a calcium increase and TRPM4 activation. Furthermore, the functional cooperation between TRPC6 and TRPM4 was indicated [59], where the stretch sensor type 1 angiotensin II receptor activates phospholipase Cγ1 by Src tyrosine kinase, leading to diacylglycerol and inositol 1,4,5-trisphosphate (IP3) formation. The stretch activates the TRPC6, which, upon opening, leads to a $Ca^{2+}$ influx and further activation of the IP3 receptor. The IP3 receptor co-localizes with TRPM4 in nanodomains [60], and the release of $Ca^{2+}$ through the IP3 receptor was shown to activate TRPM4 [54], leading to depolarization and activation of voltage gated calcium channels, $Ca^{2+}$ influx, and smooth muscle contraction. Supporting the functional cooperation, both 9-phenanthrol and the TRPC6 inhibitor larixyl acetate reduced the myogenic tone in mesenteric arteries (developed due to either KO of elastin microfibrils interface located protein-1 or the transforming growth factor β (TGF-β) treatment of wild type mice) [61]. The role of TRPM4 in the maintenance of vascular tone is supported by another study, wherein the TRPM4 inhibitor 9-phenanthrol led to the hyperpolarization of the smooth muscle cells and vasodilation [62]. Finally, TRPM4 was implicated in the coupling of P2Y4 and P2Y6 receptor-mediated mechanoactivation and myogenic tone development in cerebral parenchymal arterioles. Later on, the involvement of RhoA/Rho-associated protein kinase signaling was confirmed in the process, as the Rho-associated protein kinase inhibitor H1152 strongly attenuated, while the RhoA activator CN03 potentiated the pressure-induced constriction [63]. TRPM4 seems to be involved in the regulation of arterial tone at least in the cerebral vessels of rats, despite the lack of difference in agonist- or pressure-induced contractile responses detected in the aorta or in hindlimb preparations isolated from wild-type or TRPM4 KO mice [64]. One might argue that the different

species are the reason for the discrepancy. Moreover, the systemic KO of TRPM4 can lead to compensatory changes. It must be noted that TRPM4 KO mice were mildly hypertensive, due to the slightly increased catecholamine secretion, which can compensate for the loss of TRPM4-induced smooth muscle contractility. Unfortunately, the reports from rat TRPM4 KO animals [65][66] do not describe vascular smooth muscle function. In murine cerebral arterial smooth muscle cells, TRPM4 channels are responsible for nitric oxide-mediated vasodilation via inhibition of the PKG substrate-mediated, IP3 receptor-dependent $Ca^{2+}$ release [67].

## 2.4. The Role of TRPM4 in Chemosensation

TRPM5 is generally accepted to be involved in the olfactory system [68]. TRPM4 is expressed in murine accessory olfactory bulb mitral cells, where it mediates, at least in part, the sustained responses evoked by the calcium-activated nonselective cationic current [69]. A calcium-activated nonselective cationic current is present in the vomeronasal sensory neurons of hamsters, where it can either directly mediate vomeronasal sensory transduction or amplify the primary sensory response [70]. In mice, the TRPM4 protein was itself expressed in vomeronasal sensory neurons where its expression was estrous cycle-dependent, suggesting TRPM4 participation in the sex-specific, estrous cycle-dependent, and sex hormone-regulated functions of the vomeronasal organ [71].

TRPM5 is clearly important to taste sensation [72], but the contribution of TRPM4 in sensing sweet, bitter, and umami tastes in mice has also been suggested [73]. The TRPM4 protein was expressed in type II and type III but not type I taste cells, whereas its absence in the KO mice strain resulted in significantly impaired taste sensation. TRPM4 and TRPM5 are the only two channels mediating taste-induced $Na^+$ entry; complete loss of taste sensation was only detected in the double (TRPM4 and TRPM5) KO mice indicating the requirement of not only TRPM5 but also TRPM4 for sensation of sweet, bitter, and umami tastes [73].

## 2.5. The Role of TRPM4 in Renal Physiology

TRPM4 mRNA expression was weak in murine kidneys [74][75], but it was detected in rat [76] and human kidneys [23]. A TRPM4-like current was described in the M-1 mouse cortical-collecting duct cell line [77] and basolateral membrane fragments of murine cortical thick ascending limbs cells [78], as well as in cells of other tubular segments, including proximal (pars recta), distal convoluted, connecting and outer medullary collecting tubules, the thin descending limb, and the medullary thick ascending limb [79]. Calcium sensitivity was highest in the thin descending limb, high in the cortical thick ascending limb, lower in the medullary portions of the thick ascending limb and distal convoluted tubule, and lowest in the connecting tubule and the cortical and medullary collecting tubule. A $Ca^{2+}$-activated, non-selective current permeable for monovalent cations and inhibited by ATP, ADP, and AMP was present in the apical membrane of rat inner medullary collecting duct cells [80]. Renal ischemia-reperfusion reduced TRPM4 mRNA in rats [76]. A TRPM4-mediated current was detected on native cilia of renal epithelial murine cell line [81]. TRPM4 silencing led to a reduction in cilia length; the percentage of cells with cilia in the cell culture and TRPM4 might influence the apical $Ca^{2+}$ dynamics of these cells [81]. Finally, TRPM4 protein was detected in the mpkCCDc14 line (an immortalized mouse collecting duct principal cell), where $H_2O_2$ suppresses its

trafficking to the apical membrane [82]. These results indicate that the previously mentioned non-selective current is indeed likely to be mediated by TRPM4, although its role in renal physiology is still not known.

## 2.6. The Role of TRPM4 in Respiratory Neuronal Activity

TRPM4 can contribute to the activity of neurons controlling respiration. Flufenamic acid reduced the bursting activity of neurons in the pre-Bötzinger complex slice preparations obtained from neonatal mice, suggesting a role for a $Ca^{2+}$-activated inward cationic currents, probably mediated by TRPM4 [83]. Indeed, TRPM4 mRNA-expressing neurons were described in the pre-Bötzinger complex region of neonatal mice [84], and the TRPM4 protein was present in neurons of the pre-Bötzinger complex of the rat [85]. TRPM4 channels were modulated by calcium, calmodulin, and ADP in the pre-Bötzinger complex neurons in functionally intact slices and may become more important in times of increased respiratory activity such as hypoxia [86]. The mRNA and protein expressions of both TRPM4 and TRPC3 were shown in functionally identified glutamatergic, glycinergic, and GABAergic inspiratory pre-Bötzinger complex neurons as well as inspiratory motoneurons [87]. In addition to endogenously activated TRPM4 (likely mediating $Ca^{2+}$-activated inward cationic current), TRPC3 was also implicated as playing an essential role in respiratory pattern formation, but not in respiratory rhythm generation in both neonatal and mature rodents [87]. Some of these results were confirmed in adult mice using TRPM4-targeted short hairpin RNA, where TRPM4 suppression decreased the tidal volume but increased respiratory frequency, often followed by gasping and fatal respiratory failure [88]. The contribution of TRPC3 was questionable, which was, in all likelihood, due to the different concentrations and off-target actions of the TRPC3 inhibitor used in the two studies. Recently, TRPM4 was detected on neurons of the retrotrapezoid nucleus of the mouse and the channel was involved in large-amplitude membrane potential oscillations suggesting a role for TRPM4 in pacemaker-like firing required for basal, $CO_2$-stimulated, and state-dependent breathing [89].

## 2.7. The Proposed Role of TRPM4 in Various Other Neuronal Function

Apart from the previously mentioned role in respiratory centers, TRPM4 can be involved in other neuronal functions. TRPM4 immunoreactivity occurred in cell bodies of both vasopressin and oxytocin neurons [90]. In murine cerebellar Purkinje cells, TRPM4 (and also TPRM5) can be involved (but not be exclusively responsible) in generating a strong depolarization-induced slow, inward cation current [91]. Moreover, TRPM4 can fine-tune the $Ca^{2+}$ influx and thereby influence the firing activity of rat cerebellar granule cells [92]. TRPM4 can contribute to the persistent firing pattern of murine thalamic reticular neurons [93]. In murine CA1 pyramidal neurons, TRPM4 was only expressed on the soma at birth and its expression extended during postnatal development from the soma to the apical dendrites but not to the axon initial segment [94]. A TRPM4-like current was active at the resting membrane potential from birth and increased during development, but 10 µM 9-phenanthrol-induced current inhibition hyperpolarized the membrane potential only at later stages. TRPM4 channels are open at the resting membrane potential of the murine prefrontal cortex layer; 2/3 pyramidal neurons and their inhibition increase input resistance and hyperpolarize the membrane potential, thereby modulating neuronal excitability in a calcium-dependent manner [95]. The involvement of TRPM4 in N-methyl-d-aspartic acid (NMDA) and the receptor-dependent long-term potentiation in CA1 hippocampal neurons was also reported [96]. TRPM4, in cooperation with

NMDA receptors, can be involved in the generation of tonic and bursting activity of dopaminergic neurons in pars compacta of substantia nigra [97]. TRPM4 can also contribute to subthreshold oscillations in neurons of murine locus coeruleus and suprachiasmatic nuclei [98].

## 2.8. TRPM4 in the Heart

As shown before in many tissues, first the characterization of I($NSC_{Ca}$) was done. After the discovery of TRPM4 in many cases, it emerged as the most likely candidate for the ion channel responsible for I($NSC_{Ca}$). Several reviews detail the contribution of TRP channels to cardiovascular functions [99]. Some focus specifically on TRPM4 [100][101][102]. TRPM4 became an important player in cardiac electrical activity [103] and was involved in pathological conditions, as will be mentioned later.

### The Role of TRPM4 in Pacemaking

TRPM4 exists in nodal tissues, because TRPM4 mRNA [104] and protein [26] were detected in mice. Ion currents with TRPM4-like characteristics were detected not only in mice [26], but also in rats [27] and rabbits [27][105]. TRPM4 inhibition, achieved by 9-phenanthrol, led to a dose-dependent reduction of heart rate in wild type but not in TRPM4 KO mice, supporting an important role of TRPM4 in pacemaking [27]. It must be noted, however, that the heart rate was not reduced in TRPM KO animals compared with wild type ones [64][104][106]. These observations argue against the role of TRPM4 in pacemaking or might be the consequence of compensatory changes in the KO animals. As pacemaking is an essential function, it is highly protected by the cooperation of several mechanisms ($Ca^{2+}$ and membrane clock theories) [107]. Therefore, it is possible that, in the case of TRPM4 KO animals, the contribution of other non TRPM4-mediated mechanisms is modified in such a way that the heart rate eventually remains unchanged. On the contrary, the heart rate was significantly lower in TRPM4 KO mice but only on the surface and not the pseudo ECG [108]. In case of rabbits, 9-phenanthrol slightly but significantly reduced the spontaneous beating rate and the rate of diastolic depolarization without modifying any other AP parameters on isolated sinoatrial cells [27]. Despite these results, several questions remain to be answered as suggested by a short review [109].

### The Contribution of TRPM4 to Atrial Electrophysiology

$Ca^{2+}$-activated non-selective cation currents were reported in neonatal rat atrial myocytes [110] and isolated atrial cells from right atrial appendages [31]. Moreover, TRPM4 mRNA was detected in human atrial muscle [31]. TRPM4 protein expression was similar in human myocytes isolated from right atrial appendages of individuals both with and without atrial fibrillation [111]. The function of TRPM4 in atrial AP was characterized using the combination of TPRM4 KO mice and a pharmacological approach [32]. 9-phenanthrol- or flufenamic acid-induced TRPM4 inhibition reduced the AP duration of isolated atrial cells in a reversible and dose-dependent manner in cells from wild type but not KO animals. Other AP parameters were unaltered (except a small reduction in AP amplitude using a high (100 µM) dose of 9-phenanthrol). On the contrary, atrial AP was not modified by as high as 100 µM 9-phenanthrol when studied in intact mouse right atrial muscles [27]. Nevertheless, atrial APs were shorter in TRPM4 KO animals compared with those of wild type ones [32][104][106], except in a recent report where the only difference was a slightly

more depolarized resting membrane potential in the KO animals [108]. In congruence with previous studies where atrial APs were shorter in TRPM4 KO animals, mild (2–5 folds) and large (at least 6 folds) overexpression of TRPM4 using computer simulation led to an increase in AP duration and generation of early afterdepolarizations (EADs) [112]. These simulations were consistent with electrophysiological data obtained from the immortalized rat atrial HL-1 myocytes, where angiotensin II increased the expression of TRPM4 [112]. TRPM4 activity also increased following the functional coupling to CaMKIIδ in HL-1 myocytes [113]. In rat atrial cells, TRPM4-mediated currents could be involved in the response to shear stress via activation of type 2 IP3 receptor-mediated $Ca^{2+}$ releases [114]. TRPM4 can play a role in aldosterone-induced action potential (AP) shortening and may promote aldosterone-induced atrial arrhythmias [106]. TRPM4 was also implicated in the function of human and murine atrial fibroblasts where its expression (both mRNA and protein), as well as the ion current, increased during the culturing process, which contributed to cell growth [115].

## The Role of TRPM4 in Cardiac Conduction

TRPM4 function in atrioventricular nodal tissue was not reported, but the TRPM4 mRNA level was the highest in the Purkinje cells within the human heart [116]. The TRPM4 protein was highly expressed in the Purkinje cells of the bovine heart [29]. In rabbit Purkinje cells, 9-phenanthrol reversibly and dose-dependently shortened the APs without modifying any other AP parameters [30]. In addition, a TRPM4-like single channel current (conductance of 23.8 pS; equal permeability for $Na^+$ and $K^+$; sensitivity to voltage, $Ca^{2+}$, and 9-phenanthrol) was recorded in Purkinje cells. During the plateau phases of Purkinje AP, action potential clamp experiments revealed a transient, inward, 9-phenanthrol-sensitive current [30]. These findings indicate the contribution of TRPM4 to the AP characteristics of rabbit Purkinje cells and its potential involvement in cardiac conduction and arrhythmia generation.

Indeed, in human pathology TRPM4 mutations were first reported to be responsible for cardiac conduction disorders [117]. The first identified mutation was an amino acid change in the 7th position from glutamate to lysine (E7K), which leads to gain-of-function by reduced endocytosis and increased TRPM4-current density in the cell membrane of mainly Purkinje fibers [116]. The autosomal-dominant E7K mutation led to a progressive familial heart block type I in 3 branches of a large South African Afrikaner pedigree. The higher PIP2 sensitivity of the E7K mutant compared with wild type TRPM4 can also contribute to the gain-of-function effect [118]. Moreover, in the E7K mutant channels, the open state is much preferred, as it has increased voltage-and $Ca^{2+}$-sensitivities [119]. In computer simulations, increased E7K mutant current density led to resting membrane potential depolarization and AP prolongation. An increase of the E7K mutant (but not wild type) TRPM4-channel density also progressively reduced the AP conduction velocity, eventually culminating in a complete conduction block [119]. Three other point mutations (R164W, A432T, and G844D) with autosomal dominant inheritance in one Lebanese and two French families were associated with gain-of-function by the same mechanism: reduced endocytosis due to deregulation of Small Ubiquitin MOdifier conjugation (SUMOylation) [29]. These mutations did not influence the general biophysical characteristics of the TRPM4 current, except for an increase of $Ca^{2+}$ sensitivity in the case of G844D.

An A432T mutation was also found in congenital and childhood atrioventricular blocks, but, in contrast to the previous study, no evidence for a SUMOylation problem was detected. Moreover, the current density was smaller

and not higher than that for wild type TRPM4 [120]. A reason for the difference might be related to the different experimental conditions (recording at room temperature vs. 37 °C), as reduced expression of A432T was rescued by reducing the temperature from 37 to 28 °C [120]. Interestingly, gain-of function was detected for E7K in agreement with the study of Kruse et al. [116] suggesting that temperature sensitivity of expression is different in the case of various TRPM4 mutants. More and more TRPM4 mutations were linked to conduction problems. For instance, 13 rare mutations were detected in a study examining 95 unrelated patients of progressive cardiac conduction disease. The I376T mutation was characterized in detail and resulted in a larger TRPM4 current upon expression in human embryonic kidney (HEK) cells [121]. Another study described 6-point mutations, where 160 unrelated patients with various types of inherited cardiac arrhythmic syndromes were tested. TRPM4 mutations were found in the atrioventricular block and the right-bundle branch block but not in sinus node dysfunction, Brugada, or long QT syndrome [28]. Several TRPM4 polymorphisms, most of them in Brugada syndrome patients, were identified and based on the variable clinical phenotypes of both point mutations and polymorphisms. Stallmeyer et al. concluded that additional factors are also likely to modulate the disease phenotype in some patients [28]. Not only gain-of-function (Q854R) but also loss-of-function mutations (A101T, S1044C, and a double variant, A101T/P1204L) could lead to complete heart block [122]. A novel mutation (R819C) was described in a Chinese family with an atrioventricular block very recently [123]. Another loss-of-function mutation (G858A) was reported in a patient with a left ventricular noncompaction complicated by progressive cardiac conduction defects [124]. The link behind TRPM4 overexpression and the atrioventricular block was established by computational modeling, where the doubling of the TRPM4 currents led to EAD formation. Gaur et al. concluded that TRPM4 channels might be responsible for background sodium current, and heterogeneous TRPM4 expression in the His/Purkinje system led to a type II heart block [125].

TRPM4 mutations were reported in 6% of Brugada syndrome patients [126]. Interestingly, some of these, such as T873I and L1075P, led to gain-of-function but some, such as P779R and K914X, resulted in a reduced TRPM4 current. Any change in the resting membrane potential induced by TRPM4 mutations can reduce sodium-channel availability and contribute to Brugada syndrome. In many cases of Brugada syndrome, a mutation of the SCN5A gene leading to a change in sodium current is the reason of the conduction disorder. Moreover, a study identified the TRPM4 mutation G844D which, upon digenic inheritance with a mutation in SCN5A, was responsible for Brugada syndrome [127]. Loss-of-function TRPM4 mutations, when present in a heterozygous form, were not associated with Brugada syndrome 1 but only in the case of two mutations (compound heterozygous TRPM4 null mutations) led to a lack of TRPM4 current and Brugada syndrome [128]. Very recently, TRPM4 mutations were among the multiple genes associated with Brugada syndrome [129].

Four TRPM4 mutations, but no other mutations of the 13 major long QT syndrome genes were found in approximately 2% of the 178 patient-containing cohort [130]. The TRPM4 mutants, V441M and R499P, were almost absent in control populations, but the mechanism that describes how TRPM4 loss-of-function could lead to long QT syndrome is unknown. A more complex pleiotropic effect than merely action potential alteration was suggested. Mutations of G219E and T160M in KCNQ1 and TRPM4, respectively, were found in a 37-year-old female long QT syndrome Uygur patient [131]. Pluripotent stem cell cardiomyocytes obtained from that patient could recapitulate the electrophysiological features of long QT syndrome in vitro.

A TRPM4 structural variant identified in heterozygous deletion was suggested to be pathogenic in sudden unexplained deaths [132].

### The Contribution of TRPM4 to Ventricular Electrophysiology

The involvement of TRPM4 in ventricular AP and function is the most debated field as early reports indicated a very small expression of TRPM4 in the ventricle compared with other parts of the heart. For instance, the mRNA expression of TRPM4 was lowest in the human left ventricle [116] but was present in the right ventricle of a pediatric patient with tetralogy of Fallot [133]. Although the TRPM4 protein was expressed in murine ventricular muscle and myocytes [108], atrial expression was higher [64]. In rats, however, approximately equal expression was detected in atrial and ventricular myocytes [114]. Early reports detected TRPM4-like currents in cultured, dedifferentiated, but not native rat ventricular cells [134][135]. Moreover, a TRPM4-like current (and mRNA) was hardly detected in the left ventricular cells of Wistar rats but appeared in the left ventricular cells of spontaneously hypertensive rats [33]. Despite these abovementioned results, $Ca^{2+}$-activated non-selective cation currents were reported in cultured rat ventricular cells [1] and freshly isolated guinea-pig ventricular myocytes [136]. TRPM4 contributes to AP morphology, at least in mice, as the duration of left ventricular papillary APs was significantly smaller in TRPM4 KO mice compared with wild type ones [137]. Thereby, the increased driving force for $Ca^{2+}$ entry via L-type $Ca^{2+}$ current led to an increased contractility during β-adrenergic stimulation [137] involving the activation of adenylyl cyclase [138]. TRPM4 was involved in endurance training-induced beneficial cardiac remodeling [139]. In rats, the TRPM4 protein is clearly expressed in healthy adult ventricular myocytes [34] in contrast with the results of the Guinamard group. The reason for this difference can be the use of Wistar (or Wistar–Kyoto) rats in previous papers [33][135] while Sprague–Dawley rats have been used more recently [34][114]. Indeed, at least in mice, TRPM4 protein expression was about 80% higher in animals with a 129SvJ background versus a C57Bl/6N background [140]. Moreover, on the functional level, increased β-adrenergic inotropy was detected in global TRPM4-deficient 129SvJ mice, but the inotropic response was unaltered in C57Bl/6N mice with both global and cardiomyocyte-specific TRPM4 deletion [140].

Despite the conflicting data, TRPM4 inhibition can be a way of increasing inotropy. Recently a strategy using in vivo AAV9-RNAi-mediated silencing of cardiac TRPM4 was developed in the hope of increasing the cardiac contractility in animal models of cardiac failure, where a 90% reduction of TRPM4 protein expression was achieved in the adult mouse heart [141].

Further roles of TRPM4 in cardiac pathology will be discussed later in Section 3.7.

## 2.9. The (Potential) Roles of TRPM4 in Other Tissues

TRPM4 mRNA was detected in both human and monkey colon tissues and in colonic smooth muscle cells [11]. TRPM4 might influence the resting membrane potential and determine basal excitability of colonic smooth muscle. Similarly, TRPM4 might be involved in setting the resting membrane potential and thereby regulating the basal tone of the ileal longitudinal smooth muscle of the mice [142].

Although TRPM4 is not principally regulated by temperature, calcium-activated monovalent cation currents were described in brown adipocytes [143][144]. TRPM4 can modulate calcium signaling in human adipose tissue-derived stem cells [145]. Human adipose tissue-derived stem cells express both mRNA and a protein of TRPM4, and its knockdown (KD) inhibits histamine-evoked lipid droplet accumulation and adipocyte differentiation [19]. Similarly, TRPM4 is required for rat dental follicle stem cell proliferation and survival [146]. Moreover, TRPM4 promotes adipocyte differentiation of rat dental follicle stem cells but inhibits osteogenesis [147]. A TRPM4 mRNA reduction was found during adipocyte differentiation in murine 3T3-L1 cells [148].

TRPM4 contributes to both mucin 2 and MUC5AC secretion in HT29-18N2 colonic cancer cells, where a $Na^+/Ca^{2+}$ exchanger 2 works in concert with TRPM4 [21]. Similarly, the amount of MUC5AC secretion was reduced after the blockade of NCX2 as well as upon the application of 9-phenanthrol in differentiated normal bronchial epithelial cells and tracheal cells from patients with cystic fibrosis [21]. TRPM4 can mainly be involved in stimuli-induced but not basal mucin secretion.

Among with many other TRP channels, TRPM4 was expressed in human osteoblastic phenotype-differentiated valve interstitial cells, where TRPM4 expression was higher in calcified tissues compared with control tissues [22].

TRPM4 mRNA was shown to be present in murine testis [75]; however, its presence was not detected previously [74]. In rats, TRPM4 mRNA was detected [149]. Western blot- and immunohistochemistry-detected TRPM4 in rat spermatogenic cells and spermatozoa suggests a yet unexplored role for TRPM4 in spermatogenesis [150].

Although TRPM4 mRNA was not found in murine lungs [74], two other studies reported TRPM4 mRNA in lung tissue [75] and freshly isolated and primary cultured type II cells from rat or healthy human lungs [151]. A calcium-activated monovalent cation current with typical properties including ion selectivity, $Ca^{2+}$ dependence, and blockade by adenosine nucleotides could be mediated using TRPM4 and might reduce surfactant production.

In murine pancreatic acinar cells, a single channel current with properties of TRPM4 was present [152]. Later, TRPM4 mRNA was also detected; moreover TRPM4 was suggested to be involved in the negative feedback regulation of $Ca^{2+}$ entry [153].

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