Functional importance of T-type voltage-gated calcium channels in the cardiovascular and renal system: news from the world of knockout mice

Pernille B. L. Hansen
Department of Cardiovascular and Renal Research, Institute of Molecular Medicine, University of Southern Denmark, Odense C, Denmark
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Hansen PB. Functional importance of T-type voltage-gated calcium channels in the cardiovascular and renal system: news from the world of knockout mice. Am J Physiol Regul Integr Comp Physiol 308: R227–R237, 2015. First published December 17, 2014; doi:10.1152/ajpregu.00276.2014.—Over the years, it has been discussed whether T-type calcium channels Ca\textsubscript{v}3.1 play a role in the cardiovascular and renal system. T-type channels have been reported to play an important role in renal hemodynamics, contractility of resistance vessels, and pacemaker activity in the heart. However, the lack of highly specific blockers cast doubt on the conclusions. As new T-type channel antagonists are being designed, the roles of T-type channels in cardiovascular and renal pathology need to be elucidated before T-type blockers can be clinically useful. Two types of T-type channels, Ca\textsubscript{v}3.1 and Ca\textsubscript{v}3.2, are expressed in blood vessels, the kidney, and the heart. Studies with gene-deficient mice have provided a way to investigate the Ca\textsubscript{v}3.1 and Ca\textsubscript{v}3.2 channels and their role in the cardiovascular system. This review discusses the results from these knockout mice. Evaluation of the literature leads to the conclusion that Ca\textsubscript{v}3.1 and Ca\textsubscript{v}3.2 channels have important, but different, functions in mice. T-type Ca\textsubscript{v}3.1 channels affect heart rate, whereas Ca\textsubscript{v}3.2 channels are involved in cardiac hypertrophy. In the vascular system, Ca\textsubscript{v}3.2 activation leads to dilation of blood vessels, whereas Ca\textsubscript{v}3.1 channels are mainly suggested to affect constriction. The Ca\textsubscript{v}3.1 channel is also involved in neointima formation following vascular damage. In the kidney, Ca\textsubscript{v}3.1 regulates plasma flow and Ca\textsubscript{v}3.2 plays a role setting glomerular filtration rate. In conclusion, Ca\textsubscript{v}3.1 and Ca\textsubscript{v}3.2 are new therapeutic targets in several cardiovascular pathologies, but the use of T-type blockers should be specifically directed to the disease and to the channel subtype.

Changes in intracellular calcium concentration due to the opening of voltage-gated calcium channels are involved in contractility, excitability, exocytosis, proliferation, and many more cellular processes. The family of voltage-gated calcium channels consists of 10 subfamilies, and it is usually the L-type that is associated with vascular contractility. However, two of the three T-type channels (Ca\textsubscript{v}3.1 and Ca\textsubscript{v}3.2) are expressed in the cardiovascular and renal system, where they play a functional role. T-type channels are low-voltage-activated channels that activate after a rather limited depolarization (22), with tiny transient currents. The physiological role for T-type channels has been discussed in recent reviews (19, 32, 40, 58, 59, 74, 81). However, the use of transgenic T-type mice has led to new and surprising findings regarding the different functions of the molecular subtypes of the T-type channels Ca\textsubscript{v}3.1 vs. Ca\textsubscript{v}3.2.

On the basis of pharmacological studies, it appears that T-type channels are involved in contraction of renal resistance vessels and, thereby, affect renal function (4, 23, 33, 41, 80). But the T-type channels are also suggested to play a role in constriction in other types of blood vessels. T-type antagonists inhibit contractility in mesenteric, cerebral, and basilar arteries (9, 30, 57, 72). These data support a potential role for T-type calcium channels in regulation of vascular tone at low intravascular pressures in small resistance vessels. On the other hand, a study based on the T-type blocker Ni\textsuperscript{2+} suggested that Ca\textsubscript{v}3.2 channels could dilate the efferent arteriole of the kidney (83). T-type channels are also suggested to play a role in pacemaker activity and in atrioventricular conduction (31, 66, 68). Interestingly, clinical studies using combined L- and T-type blockers have shown a beneficial effect on high blood pressure, proteinuria, arterial stiffness, and endothelial dysfunction compared with selective L-type blockers (53, 76, 77, 79, 89). The challenge in all of these studies is the lack of selective T-type blockers. Many of the findings have, therefore, been questioned on the basis of whether or not the observed effect is due to specific inhibition of T-type channels or not. Furthermore, it has not been possible to distinguish between T-type subtypes Ca\textsubscript{v}3.1 and Ca\textsubscript{v}3.2.

The global knockout mouse models for Ca\textsubscript{v}3.1 and Ca\textsubscript{v}3.2 have provided a new way to investigate the T-type channels and their role in the cardiovascular system. (14, 60). Unfortunately, both models have neurological defects that have to be kept in mind when studying the cardiovascular system. T-type
channels are now known to be involved in vascular function being involved in ACh-induced relaxation of coronary and cerebral arteries (Ca,3.2) (14, 36) and contractility in mesenteric and pulmonary vessels (Ca,3.1) (111). Furthermore, these channels regulate heart rate (Ca,3.1) (67). Despite changes in vascular and cardiac function, blood pressure deviation has not been observed in either Ca,3.1−/− or Ca,3.2−/− mice under basal conditions. Recently, it has been suggested that T-type channels play a major role in cardiovascular pathophysiology. The Ca,3.2 T-type channel is required for pressure overload-induced cardiac hypertrophy (18), and Ca,3.1 plays a critical role in neointima formation after vascular damage (105). In addition, the use of T-type knockout mice has shown that T-type channels affect both glomerular filtration rate (Ca,3.2) and renal blood flow (Ca,3.1) (103).

This review has a functional focus: what have we learned about T-type channels from the use of knockout mice and what are the physiological and pathophysiological effects of the two T-type channel subtypes?

**Pharmacological Inhibition of Calcium Channels**

Calcium channel antagonists are widely employed as pharmacological treatments for arterial hypertension, migraines, cerebral vasospasm, atrial fibrillation, and angina pectoris. They act through the inhibition of voltage-gated calcium channels (Ca,), whereby calcium influxes are decreased and the intracellular calcium concentration is diminished. Changes in intracellular calcium concentration regulate many cellular events, such as contraction of the vascular smooth muscle cell, NO release in endothelial cells, and conductance in the sinoatrial node. The intended target for most calcium blockers is L-type channels. However, not all of the antagonists are selective for the L-subtype. The calcium channel antagonists differ in their selectivity for the various calcium channel subtypes (25, 26, 32, 82). Despite the existence of several Ca, subtypes, the physiological importance of these various calcium channels subtypes is unknown. Therefore, it is imperative to learn about drug selectivity for clinical applicability. To increase our knowledge about the functional roles of the calcium channel molecular subtypes (T-type Ca,3.1 and Ca,3.2 channels), the knockout models are of great value.

T-type Ca, channels may provide novel therapeutic targets for the treatment of obesity (107), hypertension (76), and kidney diseases, and new, commercially available drugs for T-type Ca, channels have recently emerged for therapeutic and experimental use (28, 94). Furthermore, some of the newly developed drugs are highly selective for single subtypes (27).

The advantages of using selective T-type antagonists are increasing. However, the disadvantages and concerns must also be considered. The use of T-type knockout mice has made it possible to establish the function of the T-type channels Ca,3.1 and Ca,3.2 without various calcium blockers. Hopefully, the role of T-type channels will be clarified during normal physiological conditions and in cardiovascular disease. This review presents current knowledge about T-type Ca, channels and their roles in cardiovascular and renal physiology and pathophysiology. It will establish an overview of the functional differences between Ca,3.1 and Ca,3.2 and, thereby, clarify the possible positive and negative consequences of the increased use of T-type channel blockers.

**T-type Channel and Knockout Models**

The T-type channel is formed by an α1-subunit that is the essential component necessary for the expression of a voltage-gated calcium channel, i.e., the calcium pore, the voltage sensor, and the drug-binding sites (43). The α1-subunit consists of four homologous domains (I to IV), each containing six transmembrane spanning domains (S1 to S6). Genes encoding mRNAs for the Ca, α1-subunits have been cloned, and the T-type channels include three different types of channels, with Ca,3.1 (CACNA1G gene) and Ca,3.2 (CACNA1H gene) being expressed in the vasculature. The Ca,3.1-deficient mouse was made by the laboratory of Dr. Shin (52) by deleting most of the NH2 terminus of the protein. The mice have several neurological disorders, including sleep disturbances (60) and neuropathic pain (93). However, neurological disorders are beyond the scope of this review (for review, see Ref. 17).

Dr. Campbell et al. (14) made the Ca,3.2 knockout mouse by deleting the SS segment of domain I (SSS region) of the CACNA1H gene. From this mouse, we now know that Ca,3.2 is involved in cognitive functions, such as memory (15), and the mouse exhibits several cardiovascular changes (discussed below). The knockout models have provided us with extensive information regarding channel function. However, it must also be kept in mind that these models have challenges like the existence of compensatory mechanisms. The data from the knockout mice should ideally be compared with data from pharmacological studies.

**Do T-Type Channels Affect Vascular Function?**

The electromechanical contraction coupling in blood vessels is highly dependent on the function of voltage-gated calcium channels. Thus, contraction induced by pressure and many vasoactive agonists involves voltage-gated calcium channels. Several types of calcium channels, including T-type channels, might be involved in the excitation-contraction mechanism in the blood vessels of both rodents and humans (1, 5, 33, 34, 72). Therefore, T-type channels may contribute to the regulation of peripheral vascular resistance. Two T-type channel molecular subtypes (Ca,3.1 and Ca,3.2) have been identified by molecular techniques in the rat renal (33), rat and mouse mesenteric (5, 9, 30), brain (57, 72), and rat cremaster arteries (108). Both Ca,3.1 and Ca,3.2 channels are expressed in rat, mouse, and human vascular smooth muscle cells (19, 34, 98). Furthermore, Ca,3.3 has been identified in dog basilar arteries (73).

T-type channels are low-voltage-activated channels (81). Therefore, it has been questioned whether these channels could affect vascular smooth muscle cell functionality, because vascular cells have a membrane potential around −30 to −45 mV under perfusion conditions (54, 64). However, the discovery of T-type channel splice variants at exons 25 and 26, which result in altered voltage sensitivity and steady-state kinetics, opened the possibility that T-type channels are relevant players in the membrane potential in perfused blood vessels, and these splice variants have more depolarized activation profiles (12, 21, 59, 116). Four possible splice variants (25a, 25ac, 25b, and 25bc) exist, and recent cloning studies have confirmed that the expression of splice variants differs between tissue (58). The brain expresses variant 25a, whereas 25bc is the primary splice variant present in the vasculature (58). This 25bc variant is activated and inactivated at more depolarized potentials than the 25a variant (12, 21). Furthermore, the regulation of these
channels is complex and includes trafficking and signaling complexes with other proteins. These electrophysiological and regulatory differences could result in functional differences (42, 49, 81, 95, 104, 114).

T-type channels and contraction. Ca.3.1 channels are thought to be involved in the constriction of cerebral and mesenteric vessels and renal arterioles (9, 50, 57, 83). Although the lack of specific blockers has made it difficult to confirm this hypothesis, it can now be tested in knockout models.

It is well known that the constriction of resistance blood vessels in response to increased intraluminal pressure, i.e., the myogenic response called the Bayliss effect, is initiated by the depolarization of vascular smooth muscle cells and calcium entry through voltage-dependent calcium channels (92). It has been hypothesized that T-type channels play a role in this mechanism, and through the use of transgenic models, it has now been confirmed that T-type channels are involved in the myogenic response when the intraluminal pressure is slightly increased, whereas L-type channels play a significant role at larger pressures (Fig. 3A) (6). The myogenic response of mesenteric arteries in Ca.3.1−/− mice was abolished in the 40–80-mmHg pressure range, but it was present in wild-type mice. The response to increases in pressure at 100–120 mmHg was intact in Ca.3.1−/− mice, and the arteries constricted to the same diameter as in the wild-type mice, suggesting that the contractile apparatus is intact in the knockout animals. In a pharmacological study of cerebral blood vessels using pressure myography, the effect of T-type channel blockade on myogenic tone was most pronounced at low pressure, where the vessels are more hyperpolarized (1, 59). In conclusion, Ca.3.1 channels are important for the myogenic response at arterial pressures in the 40–80-mmHg range that are relevant under resting conditions in vivo.

The T-type channel Ca.3.1 is also suggested to be crucially important for the conduction of vasoconstriction induced by hypoxia in pulmonary blood vessels (111). This response optimizes gas exchange in the lung by redirecting blood to the ventilated areas. However, during global hypoxia, the effect can lead to pulmonary hypertension. The study revealed that hypoxia leads to depolarization of the endothelial cells and a following activation of Ca.3.1 channels. This was responsible for an increased intracellular calcium concentration that led to epoxideeicosatrienoic acid (EET) release and contraction. An involvement of T-type channels and EET has also been described in mesenteric arteries, where the vasodilatory effect of 5,6-EET was absent in Ca.3.2−/− mice, whereas the response was comparable in Ca.3.1 knockout mice and wild-type mice, suggesting that in mesenteric vessels, 5,6-EET induces a vasodilatation that involves Ca.3.2 channels (11).

Recently, we perfused isolated blood vessels from wild-type and Ca.3.1 knockout mice to determine the agonist-mediated vascular effect of these channels. Two types of blood vessels were used, mesenteric and intrarenal arteries. The mesenteric vessels were mounted in a perfusion set-up, as previously described (90), and changes in luminal diameter were tested in response to increasing concentrations of phenylephrine. Both the intrarenal arteries and mesenteric arteries were mounted on a wire myograph (34), and concentration-dependent responses to the β2-adrenergic receptor agonist, phenylephrine, were tested. The results revealed significant effects of Ca.3.1 channels on vascular responses. Phenylephrine constricted the isolated perfused mesenteric vessels starting at 10−8 mol/l in a dose-dependent manner, whereas in the Ca.3.1 knockout mouse, 10−6 mol/l of phenylephrine had no effect on contractility. Furthermore, the maximal phenylephrine-induced constriction was significantly smaller in Ca.3.1 knockout mice (Figs. 1A and 3A). Therefore, we concluded that Ca.3.1 channels are involved in mesenteric blood vessel contraction to exogenous phenylephrine. In agreement with these findings on perfused vessels, we observed a decreased contraction in Ca.3.1−/− mice in response to phenylephrine during isometric contraction of mesenteric blood vessels mounted on a myograph (Figs. 1B and 3A). In both experiments, high potassium led to a similar constriction in wild-type and knockout animals. In contrast, another study showed a significantly larger norepinephrine-induced constriction in perfused mesenteric arteries from Ca.3.1 knockout mice compared with wild-type mice (6). For intrarenal arteries mounted on a wire myograph, phenylephrine contracted the blood vessels in a dose-dependent manner. However, the contraction was significantly larger in Ca.3.1−/− renal blood vessels compared with wild-type vessels (Fig. 1C). The present data show that Ca.3.1 channels are involved in setting vascular tone in mesenteric blood vessels. Furthermore, Ca.3.1 channels play a role for the vascular response in renal segmental blood vessels, although with the opposite effect to that in mesenteric vessels. Therefore, it is suggested that Ca.3.1 channels can be involved in both contraction and relaxation, and the circumstances during which one or the other effect is observed needs to be clarified. The combined results shows that more research is needed to establish the involvement of Ca.3.1 in setting the vascular tone. Several parameters could potentially affect the results; for example: Does the type of vessel matter? Does vessel size matter? Does perfusion status matter? Does oxidation status matter? Does endothelial status matter?

T-type channels have their dominant contractile effect in smaller arterioles compared with larger arteries (5, 46, 51), which might affect the results reported for T-type channel contributions to vascular tone in different studies. Furthermore, the contribution of T-type channels to vascular contractility is regulated by NO and reactive oxygen species produced by NADPH oxidase (46). In a recent study of Ca.3.1 and Ca.3.2 knockout mice, T-type channels were shown to contribute significantly more to the constriction of mesenteric arteries of wild-type mice after L-NAME treatment, an effect that was attenuated in both knockout models (46). Furthermore, T-type channels were upregulated after L-NAME treatment due to increased bioavailability of reactive oxygen species. These data suggest that T-type channels play a larger role in vascular function under conditions of oxidative stress. In agreement, T-type currents are inhibited by NO through cGMP/PKG signaling in cerebral artery smooth muscle cells, and T-type channels are, therefore, a regulatory target for NO and endothelial function (37).

T-type channels, NO production, and vasodilation. The first report about T-type channels and vasodilation came from the group of Kevin Campbell (14). They demonstrated abnormal relaxation in response to ACh and a NO donor. The Ca.3.2 knockout mouse has normal vasoconstrictor responses but reduced relaxation of coronary arteries. Because the relaxation in response to the NO donor was also impaired in the
Ca$_{3.2}^{-/-}$ mouse, it was concluded that Ca$_{3.2}$ channels affect vasodilation through a vascular smooth muscle cell-related mechanism and not directly through endothelial function and NO production. Large-conductance calcium-sensitive potassium channels (BK$_{Ca}$) located in vascular smooth muscle cells are responsible for the hyperpolarization that leads to the relaxation of the smooth muscle cells. The authors suggested that Ca$_{3.2}$ channels are coupled to BK$_{Ca}$ in smooth muscle cells, because coimmunoprecipitation showed that Ca$_{3.2}$ colocalized with BK$_{Ca}$ in brain lysates. A BK$_{Ca}$ channel opener induced similar relaxations in wild-type and knockout mice, confirming the hypothesis (Fig. 3B) (14). In agreement, Ca$_3$ channels colocalize with BK$_{Ca}$ and T-type currents are able to activate the potassium channels in rat medial vestibular neurons (85). A recent article confirms the surprising finding that activation of T-type channels (Ca$_{3.2}$) is involved in the relaxation of blood vessels (36). The article demonstrates that in rat smooth muscle cells, calcium influx through Ca$_{3.2}$ channels leads to activation of ryanodine receptors, calcium release from internal stores, activation of BK$_{Ca}$ channels, hyperpolarization, and vascular relaxation. Furthermore, evidence is presented that the same mechanism exists in human cerebral arteries (Fig. 3B) (36). Taken together, these data show that Ca$_{3.2}$ channels and BK$_{Ca}$ play an important role for vasculature calcium-dependent hyperpolarization and the following vasodilation.

Ca$_{3.2}$ channels may also be involved in the conduction of vasodilator responses in cremaster arterioles (24). It was demonstrated that electrical stimulation of isolated blood vessels leads to constriction at the local site of stimulation followed by vasodilation, which is conducted upstream. The dilation was dependent on NO release and opening of Ca$_{3.2}$ channels because the dilation was significantly reduced in both endothelial nitric oxide synthase (eNOS) and Ca$_{3.2}$-deficient mice. The authors suggested that calcium influx through T-type channels in the endothelium activates endothelial nitric oxide synthase (eNOS) and Ca$_{3.2}$-deficient mice. The dilation was dependent on NO release and opening of Ca$_{3.2}$ channels because the dilation was significantly reduced in both endothelial nitric oxide synthase (eNOS) and Ca$_{3.2}$-deficient mice. 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teric blood vessels, real-time imaging showed a diminished NO production, and cGMP formation was smaller in Cav3.1−/− mice after depolarization compared with wild-type mice (100). Interestingly, this mechanism also has in vivo effects, as the contribution of NO to the regulation of blood pressure also involves T-type channels. The eNOS inhibitor L-NAME increased the blood pressure of wild-type mice, but this was not found in Cav3.1 knockout mice (100).

T-type channels are involved in vasodilation, either directly through a smooth muscle cell activation of BKCa channels (Cav3.2) (14, 36) or through an endothelium-dependent activation of eNOS (Cav3.1) (100). As previously described, T-type channels (Cav3.1) are also involved in vasoconstriction (see Table 1) and, therefore, a potential target in cardiovascular disease. However, the dilatory effect needs to be taken into account when T-type blockers are considered for the treatment of obesity (107), hypertension (76), cancer (102), and diabetic nephropathies, as treatment with T-type blockers could have vasoconstrictor effects in humans. This effect could have an adverse clinical impact when patients are treated with combined L-type and T-type blockers instead of a selective L-type blocker. However, clinical studies demonstrated that T-type blocker treatment protects against endothelial dysfunction and arterial stiffness and suggested that T-type blockade has protective effects, despite the involvement of dilatory mechanisms (53, 79). The channels are also involved in vasoconstriction and inflammation (117), as described previously, and if these contractile effects predominate, they could be the cause of the protective effect.

Vascular pathology. The T-type channels might be of significant cardiovascular disease that is characterized by endothelial dysfunction with decreased NO production, because T-type channels are upregulated in the arterial stiffness and suggested that T-type blockades have protective effects, despite the involvement of dilatory mechanisms (53, 79). The channels are also involved in vasoconstriction and inflammation (117), as described previously, and if these contractile effects predominate, they could be the cause of the protective effect.

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Fig. 2. Depolarization-induced constriction and subsequent dilation in mouse mesenteric arteries. Isolated mesenteric arteries were perfused from Cav3.1−/− mice and C57BL/6 (WT) mice, and changes in luminal diameter were determined after administration of K+ (70 mM). The analysis was by two-way ANOVA followed by Bonferroni analysis comparing genotype and time. Data are expressed as means ± SE (n = 27) *P ≤ 0.05. [Modified with kind permission from Springer Science+Business Media: Pflügers Arch. 466: 2205–2214. 2014. Svenningsen P, Andersen K, Thuesen AD, Shin HS, Vanhoucke PM, Skott O, Jensen BL, Hill C, Hansen PB. Fig. 1A] (100).

activity in the renin angiotensin system (55, 109) and increased oxidative stress through the activation of NOX enzymes. These mice have an increased expression of T-type channels, and the channels contribute to a larger extent to the vascular tone compared with nonhypertensive wild-type animals (45). It is, therefore, plausible that T-type channels play a greater role in vascular responses during cardiovascular events compared with normal physiology. This hypothesis should be further explored.

Over the years, it has been discussed whether T-type channels play a role in vascular injury and subsequent neointima formation. The T-type channel antagonist mibebradil prevents neointima formation after vascular injury in rats (proliferation in vivo and in vitro was inhibited by mibebradil, but not by the more selective L-type calcium channel blockers verapamil and amlodipine) (91). In contrast, Quignard et al. (84) concluded that T-type channels are not involved in vascular injury, as they could not measure any T-type currents in vascular smooth muscle cells isolated after balloon injury. The use of transgenic mouse models has made it possible to answer this question. Thus, data from T-type Cav3.1−/− mice address that T-type channels are involved in the vascular injury response (105). Cav3.1−/− mice were protected against neointima formation after wire-induced vascular injury, while Cav3.2 and wild-type mice were not. Interestingly, a T-type antagonist, NNC55–0396, also inhibited neointima formation, and the authors suggested that Cav3.1 may be a potential therapeutic target to prevent vascular restenosis. Furthermore, Cav3.1 mRNA and protein expression are upregulated in the injured carotid artery and are localized to neointimal vascular smooth muscle cells...
(105). In agreement, T-type channels are predominantly expressed in the G1 and S phase of the cell cycle and not in the G0 phase in rat aortic smooth muscle cells (56), and therefore, they are associated with the proliferative state. Furthermore, Cav3.1 channels may be responsible for the calcium influx leading to cell proliferation (105), and pharmacological blockade of Cav3.1 channels inhibits proliferation of human pulmonary vascular smooth muscle cells (86).

The Cav3.1 and Cav3.2 transgenic mouse models allow us to investigate the contribution of these channels to the regulation of vascular tone, endothelial function, remodeling, arterial stiffness, and blood pressure, all of which are aspects of cardiovascular disease profiles (Table 1). The results from these types of studies will be interesting to follow, and clinical studies have already indicated that T-type blockers could be a relevant tool for treating endothelial dysfunction (53, 79), hypertension (76), and arterial stiffness (89). The protective effect of T-type channels on endothelial function was determined by measurement of flow-mediated vasodilation and nitroglycerin-induced vasodilation in the brachial artery in 40 patients with essential hypertension. Treatment with efonidipine (T- and L-type Ca\(^{2+}\) channel blocker) or with nifedipine (L-type Ca\(^{2+}\) channel blocker) showed that the endothelial function index was significantly augmented by efonidipine but unchanged by nifedipine (79). On the basis of the suggested protective effects of T-type channels, the exact role for T-type channels in cardiovascular disease and the therapeutic potential of these drugs need to be established in the years to come. Results from the knockout animals lead to the conclusion that vascular pathologies with increased oxidative stress and/or cell proliferation can lead potentially to T-type channel-dependent damage of the blood vessels.

**T-Type Channels and the Heart**

*Regulation of heart rate.* T-type channels are well known to be expressed in the conduction system of the heart, and Ca\(^{2+}\) channels are expressed in both the sinoatrial and atrioventricular nodes, which suggests that Ca\(^{2+}\) channels play a role in the generation of pacemaker potentials (7, 31) (although L-type channels also play a role in pacemaker activity). L-type calcium channels are highly expressed in myocytes and are responsible for the Ca\(^{2+}\) influx initiating contraction. In contrast, T-type calcium channels are only expressed in neonatal myocytes and are not expressed in adult myocytes except for those of the conducting system (65). However, T-type channels are reexpressed in adult hypertrophied myocytes (18, 69, 75).

The putative involvement of T-type channels in the control of cardiac function is of great importance (31, 48) and, therefore, should be extensively examined in Ca\(^{2+}\), knockout mice. Ca\(^{2+}\), channels do not seem to play a significant role in the generation of pacemaker potentials. This conclusion is based on data from the Ca\(^{2+}\)-deficient mouse, which has a normal heart rate, with no arrhythmias (14). In contrast, mice lacking the Ca\(^{2+}\) channel have decreased pacemaker activity and atrioventricular conduction compared with wild-type mice (67). It was concluded that the observed bradycardia arose from a direct contribution of Ca\(^{2+}\), channels in the setting of cardiac pacemaker activity, through diastolic depolarization in the sinoatrial node and in the propagation of the impulse conduction through the atrioventricular node.

Heart rate is regulated by sympathetic activity and the β-adrenergic system. Li et al. (62) investigated a potential role for β-adrenergic receptor regulation of Ca\(^{2+}\), and heart rate. They found that a β-adrenergic agonist, isoproterenol, activated Ca\(^{2+}\), through a protein kinase in sinoatrial node cells. Isoproterenol had no effect in Ca\(^{2+}\), knockout mice, but the same effect in wild-type and Ca\(^{2+}\), knockout mice. Chen et al. (13) investigated central sympathetic activity and T-type channels in a preparation of brain stem-spinal cord-splanchnic sympathetic nerves from neonatal rats. They demonstrated that Ca\(^{2+}\), channels were required for maintaining central sympathetic outflow, and Ca\(^{3+}\) was inhibitory (13). In a clinical study with hypertensive patients and healthy subjects, T-type inhibition by efonidipine reduced the heart rate and sympathetic nervous activity (35). This effect could be due to Ca\(^{2+}\), channel inhibition as Chen et al. (13) found a role for Ca\(^{2+}\), channels in sympathetic nervous activity. However, Ca\(^{2+}\), knockout mice have normal blood pressure and heart rate. Ca\(^{3+}\) channels may, therefore, be the target involved in the pharmacological response to efonidipine.

In conclusion, the described data show that T-type channels are directly involved in setting heart rate and that the channels also affect sympathetic nerve activity. It adds to the suggested positive effects of T-type blockers but now with the focus on heart rate (Table 2). T-type channel blockers, probably of the Ca\(^{3+}\) type, have potential roles not only in vascular pathologies, but also in cardiac diseases that require heart rate reduction, such as cardiac ischemia and coronary heart disease.

Cardiac hypertrophy. Cardiac hypertrophy is a compensatory response to hypertension. In the heart, changes in calcium concentration are involved in contraction and signaling, including responses controlling myocyte growth. T-type voltage-gated calcium channels (Ca\(^{3+}\), and Ca\(^{3+}\)) are reexpressed in hypertro-
phied heart myocytes. The involvement of the different types of T-type channels, Cav3.1 and Cav3.2, has been investigated using knockout mice in models of pressure-induced cardiac hypertrophy (18, 70). Thoracic aortic constriction and ANG II infusion led to hypertrophied hearts only in Cav3.1 knockout and in wild-type mice and was absent in Cav3.2 knockout mice (18). These findings demonstrated that cardiac hypertrophy involves the activation of calcineurin/NFAT through activation of Cav3.2 channels. Furthermore, it was recently shown that an increase in Cav3.2 expression precedes cardiac hypertrophy and that the channels are activated by the transcription factor early growth response 1, Egr1 (47).

While Cav3.2 is involved in the development of cardiac hypertrophy, Cav3.1 channels are suggested to have a protective role (70). Several models of hypertrophy have demonstrated the expression of T-type channels in myocytes, and Cav3.1 knockout mice displayed an enhanced hypertrophy, which was absent in mice overexpressing Cav3.1. Cav3.1 and eNOS were colocalized in cardiac myocytes. Cav3.1 activation and subsequent cGMP production dependent on eNOS activation protects the heart against hypertrophy (70). The mechanism occurred independent of eNOS phosphorylation, implying that an increase in calcium concentration directly activates the enzyme.

In conclusion, T-type channels are involved in remodeling of the heart (Table 2). The two subtypes of T-type voltage-gated calcium channels initiate different responses that are related to their ability to change intracellular calcium concentration, with Cav3.1 being protective of hypertrophy and Cav3.2 inducing cardiac hypertrophy. Cardiac fibrosis. The impaired relaxation of the coronary vessels in Cav3.2 knockout mice described previously leads to increased cardiac fibrosis. Campbell et al. (14) demonstrated that the Cav3.2<sup>−/−</sup> mouse has significantly more fibrosis in the ventricular wall of the heart compared with wild-type mice. The size of the fibrotic area increased with age and necrosis, and lymphocyte infiltration was observed in the knockout animals. Furthermore, the structure of the coronary vessels was abnormal in these mice, being irregular in shape and more constricted. In contrast to the data from genetically modified mice, investigations using T-type blockers have shown that inhibition of Ca<sub>3</sub> channels is protective against fibrosis in models of renal injury and cardiac failure (88, 99, 115). The reason for this discrepancy is not clear. However, it might be due to the inhibition of Ca<sub>3.1</sub> channels in the pharmacological studies, as calcium blockers such as benidipine, inhibit both Ca<sub>3.1</sub> and Ca<sub>3.2</sub> (26). Another more likely possibility is that the impaired relaxation in the Cav3.2 knockout mouse leads to impaired blood supply to the heart, which is the cause of the fibrosis. The protective effect of the blockers against fibrosis could, therefore, reflect a direct T-type channel involvement in fibrosis. However, future studies are needed to clarify the involvement of the role of the T-type channels in fibrosis.

**Table 2. Cardiovascular and renal effects of deletion of Cav3 channels**

<table>
<thead>
<tr>
<th>Functional Change in the</th>
<th>Ca&lt;sub&gt;3.1&lt;/sub&gt;</th>
<th>Ca&lt;sub&gt;3.2&lt;/sub&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart and blood pressure</td>
<td>Protective role in cardiac hypertrophy (65)</td>
<td>Cardiac hypertrophy (17)</td>
</tr>
<tr>
<td></td>
<td>Pacemaker activity and atrioventricular conduction (62)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Obesity (101)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>NO-dependent blood pressure regulation (94)</td>
<td></td>
</tr>
<tr>
<td>Kidney</td>
<td>Controlling the renal plasma flow (97)</td>
<td>Regulation of GFR though an efferent arteriolar dilatation (97)</td>
</tr>
</tbody>
</table>

**Blood Pressure**

The blood pressure of both Ca<sub>3.1</sub> and Ca<sub>3.2</sub> knockout mice has been measured, and no differences in either strain were observed (18, 67). However, a decreased heart rate was observed in the Ca<sub>3.1</sub> mice, which suggests that a compensatory mechanism to normalize the blood pressure occurs in these mice. T-type channels might affect blood pressure in challenged situations, such as hypertension and metabolic syndrome. Ca<sub>3.1</sub> knockout mice are resistant to weight gain induced by a high-fat diet. In agreement, a T-type calcium antagonist decreased weight gain in wild-type mice (107). T-type channels are suggested to be the link in central regulation of vigilance to body weight. Because calcium channel antagonists are already used to treat hypertension, the use of T-type antagonists might also have favorable effects in these patients, and T-type channels could be a novel therapeutic target for obesity treatment.

Blood pressure is regulated by sympathetic input (discussed in a previous section “heart rate”) and by hormones, in particular, the renin-angiotensin-aldosterone system (RAAS). Calcium channel blockers play an important role for RAAS because T-type channels are involved in aldosterone release (16, 87). Additionally, the T-type antagonist efonidipine lowers aldosterone plasma levels in healthy volunteers (78) and hypertensive patients (101). Furthermore, the T-type blocker benidipine decreases albuminuria and plasma aldosterone in chronic kidney disease patients (3). T-type calcium channel blockers also affect the renin part of RAAS, as they inhibit renin secretion (110). The RAAS effect after T-type inhibition should, therefore, also be considered when T-type channels and blood pressure regulation are discussed.

The involvement of T-type channels in mice with challenged blood pressure regulation demonstrate that Ca<sub>3.1</sub> channels are involved in NO-mediated blood pressure regulation. Ca<sub>3.1</sub> knockout mice do not respond to NOS inhibition in contrast to their wild-type littermates, which respond with a significant increase in blood pressure (100).

In clinical studies, T-type channel blockers decrease blood pressure to a lower extent than L-type blockers (76, 77, 89). The effect of L- and T-type calcium blockers on hypertension was investigated in a changeover (ABC) study in 58 hypertensive patients. It was concluded that treatment with a combined L- and T-type antagonist (benidipine) yields greater efficacy than amlodipine (L-type antagonist) in reducing blood pressure and proteinuria (76). The involvement of T-type channels in the regulation of blood pressure in hypertensive knockout mouse models should be examined in the future. Furthermore, tissue-specific knockout of either Ca<sub>3.1</sub> or Ca<sub>3.2</sub> from the vascular smooth muscle cells or endothelium would be helpful...
in drawing a conclusion regarding the involvement of T-type channels in blood pressure regulation.

**Kidney**

T-type channels are expressed in renal resistance vessels (33) and can, therefore, potentially affect renal blood flow, glomerular filtration rate, and blood pressure, as the afferent arteriole and the efferent arteriole control renal blood flow, glomerular ultrafiltration pressure, and the distribution of flow within the kidney. Several recent reviews have looked into the pharmacological effects of T-type blockers (see Refs. 32, 38, 40, 44).

Both L-type (Ca$_{1.2}$) and T-type (Ca$_{3.1}$ and Ca$_{3.2}$) calcium channels are expressed in the renal preglomerular vessels, whereas postglomerular cortical efferent vessels are devoid of L-type channels (33), but mouse efferent arterioles express T-type (Ca$_{3.1}$ and Ca$_{3.2}$) channels. In contrast to the expression data, a recent study found no T-type currents in either afferent or efferent arteriole rat myocytes (97), although high-voltage-activated currents were observed in smooth muscle cells isolated from afferent arterioles. T-type currents were detected in the tail arteries in the same study (93). T-type currents have previously been measured in rat preglomerular vascular smooth muscle cells (29).

However, this discrepancy might be explained by the heterogeneous population of cells (29). Pharmacological studies have suggested T-type calcium channel regulation of blood vessel diameter in both afferent and efferent arterioles (23, 33, 80, 83), and L-type channels are assumed not to play a role in cortical efferent arteriolar contractility (10, 33, 63, 71). These findings suggest that T-type channels are present in efferent arterioles from mouse and man and, therefore, make the efferent arteriole an optimal choice for studying T-type channels and vascular reactivity. In the isolated perfused mouse efferent arteriole, Ca$_{3.1}$ channels may be involved in vasoconstriction, whereas Ca$_{3.2}$ channels may be involved in vasodilation (83).

Renal hemodynamics was recently studied in Ca$_{3.1}$- and Ca$_{3.2}$-deficient mice (103). Ca$_{3.2}$ channels lower the resistance of the efferent arteriole and, thereby, affect glomerular filtration rate (GFR), as Ca$_{3.2}$ knockout animals have larger contractile responses in the efferent arteriole in response to depolarization and augmented GFR with similar plasma flow. In contrast, Ca$_{3.1}$ knockout animals have larger plasma flow, and GFR remains unchanged, which is in agreement with a decreased resistance along the renal resistance vessels. However, no changes in contractility responses were observed in isolated perfused afferent and efferent arterioles from Ca$_{3.1}$ knockout mice compared with wild-type mice (103). The augmented renal plasma flow in the knockout animals could, therefore, also result from decreased renal sympathetic activity. Ca$_{3.1}$ has an inhibitory effect on the central sympathetic outflow in neonatal rats (13), which suggests that augmented activity in the knockout mouse would be expected to decrease the renal plasma flow. However, renal sympathetic activity could be substantially different because the sympathetic outflow is differentially regulated. The final conclusion on the involvement of the sympathetic system in the regulation of renal plasma flow must await further studies on renal nerve activity in mice lacking Ca$_{3.1}$ channels. The myogenic response is especially important in the kidney as a mechanism protecting the fragile glomerulus from fluctuations in pressure. As has been described, T-type channels are involved in setting the myogenic tone in mesenteric vessels (6), and it would, therefore, be interesting to investigate the potential role for T-type channels in the renal afferent arteriole. In conclusion, Ca$_{3.2}$ channels are involved in renal efferent arteriole dilation and normal GFR maintenance, whereas Ca$_{3.1}$ channels are involved in setting the vascular resistance and, thereby, renal plasma flow. These pharmacological results and transgenic models establish that T-type calcium channels contribute significantly to the regulation of renal hemodynamics (Table 2).

A recent meta-analysis of 24 studies have shown that T-type blockers significantly decline proteinuria and the urinary albumin-to-creatinine ratio compared with L-type blockers, suggesting an important involvement of T-type channels for renal function (61). Altered function of the kidney vascular segments is involved in several pathological conditions, such as diabetes and hypertension (20, 96). Several studies have suggested that T-type channel blockers have superior renoprotective effects compared with conventional calcium blockers. T-type blockers could be an additional tool for treating hypertensive proteinuric kidney disease (32). The T-type antagonist efundipidine slows the progression of proteinuric kidney disease in a manner similar to angiotensin-converting enzyme inhibitors (39), and proteinuric treatment with a combination of L- and T-type antagonists yields greater efficacy than the L-type antagonist alone (76, 77, 89). Furthermore, Sugano et al. (99) have shown in subtotal nephrectomized rats that the specific T-type antagonist R(-)-efundipidine significantly reduced proteinuria and tubulointerstitial fibrosis. The treatment of hypertension with calcium antagonists is currently not recommended in patients with kidney disease. The treatment strategy may change if the favorable effects of T-type calcium antagonists on renal hemodynamic and kidney morphology observed in animal experiments can be extended to humans. Therefore, it could be of great interest to investigate the kidney function of T-type channel knockout mice under pathophysiological conditions.

**A Therapeutic Potential for T-Type Blockers?**

The current discussion about T-type channel-mediated effects in the cardiovascular system clearly demonstrates the potential beneficial effects of T-type antagonists. However, some undesired effects might also occur and need to be considered before these drugs are clinically applied. Previously, in the cardiovascular and renal systems, the focus has been on T-type vs. L-type inhibitors. However, the two T-type channels (Ca$_{3.1}$ and Ca$_{3.2}$) clearly exert different effects on the heart, kidney, and vasculature. For example, as Ca$_{3.2}$ T-type channels are involved in the pathogenesis of cardiac hypertrophy, Ca$_{3.2}$ voltage-gated calcium channels could be considered a potential target, whereas Ca$_{3.1}$ channels may be protective against hypertrophy and, therefore, not a target. In contrast, Ca$_{3.1}$-specific antagonists might be beneficial after vascular damage because Ca$_{3.1}$ channels are involved in neointima formation. Furthermore, the direct effects on the vasculature suggest that T-type channels could play a role in vascular pathophysiology, such as endothelial dysfunction. Additionally, the effects on glomerular filtration rate suggest that T-type channels should be considered for kidney disease treatment. Further studies, especially human studies, are needed to clarify the potentially beneficial and detrimental effects of Ca$_{3.1}$ and Ca$_{3.2}$ channels. In conclusion, T-type
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channels are potential new therapeutic targets in cardiovascular pathologies, but the current review establishes the necessity to distinguish between the two subtypes when T-type blockers are considered as potential therapeutic targets.

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No conflicts of interest, financial or otherwise, are declared by the author.

AUTHOR CONTRIBUTIONS

Author contributions: P.B.H. conception and design of research; P.B.H. analyzed data; P.B.H. interpreted results of experiments; P.B.H. prepared figures; P.B.H. drafted manuscript; P.B.H. edited and revised manuscript; P.B.H. approved final version of manuscript.

REFERENCES


19. Furukawa T, Nukada T, Namiki Y, Miyashita Y, Hatsumo K, Ueno Y, Yamakawa T, Ishiihi T. Five different profiles of dihydropyridines in blocking T-type Ca2+ channel subtypes (Ca(V)3.1 (alpha1G), Ca(v)3.2 (alpha1H), and Ca(v)3.3 (alpha1I)) expressed in Xenopus oocytes. Eur J Pharmacol 613: 100–107, 2009.


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Review

Kuo IY, Ellis A, Seymour VA, Sandow SL, Hill CE.

57. Jensen LJ, Holstein-Rathlou NH.


42. Hayashi K, Wakino S, Sugano N, Ozawa Y, Homma K, Saruta T.

40. Hayashi K, Kumagai H, Saruta T.

37. Kuga T, Kobayashi S, Hirakawa Y, Kanaide H, Takeshita A.


54. Ishida T, Ishida M, Yoshizumi M, Kambe M.

53. Ishida T, Ishida M, Yoshizumi M, Kambe M.

52. Ishida T, Ishida M, Yoshizumi M, Kambe M.

51. Ishida T, Ishida M, Yoshizumi M, Kambe M.

50. Ishida T, Ishida M, Yoshizumi M, Kambe M.

49. Ishida T, Ishida M, Yoshizumi M, Kambe M.

48. Ishida T, Ishida M, Yoshizumi M, Kambe M.

47. Ishida T, Ishida M, Yoshizumi M, Kambe M.

46. Ishida T, Ishida M, Yoshizumi M, Kambe M.

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43. Ishida T, Ishida M, Yoshizumi M, Kambe M.

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36. Ishida T, Ishida M, Yoshizumi M, Kambe M.

35. Ishida T, Ishida M, Yoshizumi M, Kambe M.

34. Ishida T, Ishida M, Yoshizumi M, Kambe M.

33. Ishida T, Ishida M, Yoshizumi M, Kambe M.

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31. Ishida T, Ishida M, Yoshizumi M, Kambe M.

30. Ishida T, Ishida M, Yoshizumi M, Kambe M.

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4. Ishida T, Ishida M, Yoshizumi M, Kambe M.

3. Ishida T, Ishida M, Yoshizumi M, Kambe M.

2. Ishida T, Ishida M, Yoshizumi M, Kambe M.

1. Ishida T, Ishida M, Yoshizumi M, Kambe M.


Svensningsen P, Andersen K, Thuesen AD, Shin HS, Vanhoutte PM, Skott O, Jensen BL, Hill C, Hansen PB. T-type Ca channels facilitate NO-formation, vasodilatation and NO-mediated modulation of blood pressure. Pfliigers Arch 466: 2205–2214, 2014.


