REVIEW ARTICLE

Cardiovascular K_{ATP} channels and advanced aging

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With advanced aging, there is a decline in innate cardiovascular function. This decline is not general in nature. Instead, specific changes occur that impact the basic cardiovascular function, which include alterations in biochemical pathways and ion channel function. This review focuses on a particular ion channel that couple the latter two processes, namely the K_{ATP} channel, which opening is promoted by alterations in intracellular energy metabolism. We show that the intrinsic properties of the K_{ATP} channel changes with advanced aging and argue that the channel can be further modulated by biochemical changes. The importance is widespread, given the ubiquitous nature of the K_{ATP} channel in the cardiovascular system where it can regulate processes as diverse as cardiac function, blood flow and protection mechanisms against superimposed stress, such as cardiac ischemia. We highlight questions that remain to be answered before the K_{ATP} channel can be considered as a viable target for therapeutic intervention.

Keywords: *ATP-sensitive K^+ channel*; *ion channels*; *cardiovascular*; *aging*; *smooth muscle*

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Cardiovascular health declines with aging. Elderly patients are more likely to suffer from conditions such as atherosclerosis, ischemic heart disease, hypertension and heart failure (1). Cardiovascular disease remains the leading causes of death in most of the developed countries, with advanced age as a top risk factor. The number of aged people is expected to increase over the next decades. In the United States, for example, it is estimated that the elderly will soon comprise about 20% of the overall population (2). However, even in the absence of these underlying diseases, the aging heart undergoes intrinsic and poorly understood functional decline (3–5). The overall decline in cardiac function, however, is not a general phenomenon but appears to be caused by specific alterations in diverse biochemical and electrophysiological pathways. These aging-related changes have been well-documented in the literature and will only be briefly discussed here. For a more complete analysis, the reader is referred to reviews on this subject elsewhere (4,6–8). For potential therapeutic reasons, it is imperative to understand the cardiovascular decline during advanced aging and the mechanisms of cardiovascular diseases, when superimposed on this functional deficit.

Aging-associated electrophysiological and cellular changes

There is a decline in cardiovascular function during advanced aging in certain biochemical and cellular pathways (9). Specific changes in cardiomyocyte function include smaller contractions (10), due largely to alterations in intracellular Ca^{2+} handling. In some studies, the L-type Ca^{2+} current was described to be reduced with advanced age, which would lead to less Ca^{2+} release from the sarcoplasmic reticulum (SR) and a smaller contraction amplitude. The rate with which Ca^{2+} is released from the SR is also slower, which explains a prolonged time-to-peak of the cardiac contraction. Relaxation occurs as the Ca^{2+} is taken back up into the SR by the action of the SR Ca^{2+} pump, sarco/endoplasmic reticulum Ca^{2+}-ATPase (SERCA). Since SERCA levels and activity are decreased with advanced age, the relaxation rate of the cardiac contraction is also impaired (2). For a detailed description of cardiac excitation contraction performance with advanced age, see the review by Feridooni et al. (10).

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The action potential of cardiomyocytes is caused by the action of ion channels, exchangers and pumps. The shape and duration of the action potential (important determinants of contractility), heart rate and arrhythmogenesis are determined by a coordinated interplay between all of these ion translocating systems. At least some of these are specifically altered during advanced aging, which explains the prolonged action potential duration that occurs (5,10). There is no general agreement on the exact nature of the changes in individual ion channel currents, but in general a decrease in outward K^+ currents, such as the transient outward K^+ current (I_{to}) (5), would suffice to explain a prolonged action potential. Age-dependent changes in the slowly activating delayed rectifying K^+ current (I_{Ks}) and the Na^+–Ca^{2+} exchanger (NCX1) have also been reported by some investigators (10).

ATP-sensitive K^+ channels

A class of K^+ channels, which open in response to metabolic demand and stress, has initially been described in cardiac myocytes (11). They are able to couple intracellular energy metabolism to electrical excitability due to their sensitivity to the levels of cytosolic high-energy nucleotide molecules (12). Specifically, their opening probability is increased when there is a decline in intracellular ATP and an increase in ADP and AMP levels. As the channel was initially characterized by its sensitivity to intracellular ATP, it has been named the ATP-sensitive K^+ (K_{ATP}) channel.

Molecular components of K_{ATP} channels

There are several classes of K_{ATP} channels throughout the body, and they differ from each other in terms of their electrophysiological profiles, their sensitivities to intracellular nucleotides (ATP and ADP) and to specific pharmacological compounds that act on these channels (13). With the molecular cloning of the components of K_{ATP} channels, it has become apparent that these differences are due largely to the specific combinations of the different subunits. The K^+-permeable pore-forming component of the channel if formed by the Kir6.1 or Kir6.2 subunits, which combine with the drug-sensitive sulfonylurea receptors, SUR1 or SUR2 (12). Two major SUR2 alternative spice variants (SUR2A and SUR2B) are commonly studied. Thus, channels that are composed of Kir6.1/SUR2B subunits (such as those found in vascular smooth muscle) behave quite differently to those, for example, which are formed by Kir6.2/SUR2A subunits (as might be found in ventricular myocytes) (12).

Cardiac K_{ATP} channels
The native K_{ATP} channel in cardiac ventricular myocytes
In vitro, the metabolic state of a resting isolated cardiomyocyte is sufficient to keep the K_{ATP} channel closed.

As a result, K_{ATP} channel blockers (such as glibenclamide and tolbutamide) have little or no effect on the cardiac action potential during patch clamp experiments. In a beating heart, however, which has a much higher metabolic demand, the physiological role of K_{ATP} channels is more apparent. For example, with an elevated heart rate, the action potential gradually shortens over a period of several minutes. This frequency-dependent adaptation of the action potential duration is prevented by blocking K_{ATP} channels with glibenclamide or by suppressing the channel genetically with cardiac-specific overexpression of dominant-negative Kir6 subunits (14). Presumably, therefore, the elevated metabolic demand associated with an increased heart rate (as occurs during exercise) is sufficient to stimulate K_{ATP} channel opening, which in turn causes the action potential to shorten.

Effects of aging on the ventricular K_{ATP} channel
The ventricular K_{ATP} channel is inhibited during advanced aging (15,16). In one study, the amount of whole-cell current that is activated with a K_{ATP} channel opener, pinacidil, was found to be smaller in ventricular myocytes isolated from 18-month-old female (but not male) guinea pigs when compared to those from 8-week-old animals (15). In another study, in which maximal K_{ATP} channel opening was achieved by metabolic blockade with 2-4 dinitrophenol (DNP), the K_{ATP} channel density was reported to be significantly depressed in ventricular myocytes isolated from 28- to 30-month-old Fischer 344 male rats (when compared to 5-month old) or from 30-month-old C57BL/6 male mice (compared to 4- to 6-month-old males) (16). The reasons for the apparent gender differences between these two studies may be due to species differences or the age of the animals. The rat and mouse studies were performed at an age where 50% mortality occurs (about 24 months for the Fischer male rat and C57BL/6 mice). In contrast, the 18-month-old guinea pigs were at a relatively young age, since 50% mortality occurs at about 45 months for male guinea pigs (17). Thus, the K_{ATP} channel may well be inhibited in both male and female guinea pigs when studied at a more relevant older age. These two studies show a decreased whole-cell K_{ATP} channel current density, but this observation does not clarify the mechanism. For example, this result may be due to a decreased sensitivity of the K_{ATP} channel to metabolic inhibition and pinacidil. A more likely explanation, however, is that the density of sarcolemmal K_{ATP} channels is decreased. Indeed, there is a smaller number of K_{ATP} channels in an excised membrane patch isolated from aged Fischer 344 rat ventricular myocytes when compared to the young group (16).

In addition to the decreased number of surface K_{ATP} channels, interesting and important changes occur in the channel's sensitivity to inhibitory nucleotides since K_{ATP} channels from the aged rodent heart were more

sensitive to the inhibitory effect of ATP (16). An interesting change occurred in the nucleotide sensitivity. Normally, the relationship between the ATP concentration and K$_{ATP}$ channel activity can be described by a modified Hill equation (18). In aged hearts, however, ATP inhibition was best described by assuming a model where two ATP binding affinities contribute to the overall ATP sensitivity (16). ATP binds to the Kir6.x subunit to inhibit channel activity (12), but the K$_{ATP}$ channel's ATP sensitivity is determined by its overall composition (12,19,20). The possibility is therefore raised that age-dependent changes occur in the molecular makeup of K$_{ATP}$ channels, but this idea remains to be investigated experimentally. Regardless of the underlying mechanism, the consequences remain the same: not only are there fewer channels per unitary surface area, but they are also more readily closed at physiological ATP concentrations. The result would be that substantially fewer channels are available for biological activity.

Apart from the intrinsic changes in ventricular K$_{ATP}$ channel function and ATP sensitivity, one must also consider implications of its regulation. Given that the K$_{ATP}$ channel directly senses and responds to changes in intracellular nucleotides, changes in energy metabolism during advanced again may directly affect the ATP:ADP ratio, and hence K$_{ATP}$ channel open probability. There are important biochemical changes that occur in the aging heart, which is a topic beyond the scope of this review and the reader is referred to reviews on this subject (21,22). Not only is mitochondrial metabolism affected, but also defects occur in glucose uptake and glycolytic ATP production (23–29). The limited availability of glycolytic ATP may be particularly important for K$_{ATP}$ channel function, given that glycolysis preferentially regulates the ventricular K$_{ATP}$ channel (30,31) and that glycolytic enzymes are key components of the K$_{ATP}$ channel megadalton complex (32–34). Thus, alterations in glycolytically produced ATP might have significant effects on K$_{ATP}$ channels during advanced aging. This issue may become even more important during early ischemia, when both K$_{ATP}$ channel opening and glycolysis may have protective effects (12,35). The interplay between these events in the aging heart, however, remains to be elucidated.

Vascular K$_{ATP}$ channels
The native channel in blood vessels
K$_{ATP}$ channels in coronary arterial smooth muscle help to maintain constant blood flow to the myocardial tissue (36,37). They regulate coronary flow alterations in response to metabolic demand (38). Their contribution to regulating membrane potential of smooth muscle cells (and thus blood flow) increases as the coronary diameter decreases along the vascular bed, consistent with a significant role for K$_{ATP}$ channels in smaller resistance vessels. Coronary smooth muscle K$_{ATP}$ channels also

contribute to the maintenance of flow in the coronary microvasculature in response to changes in blood pressure (autoregulation). Vascular K$_{ATP}$ channels exist in two forms: there is evidence for a small/medium conductance channel, with a unitary conductance ranging between 10 and 50pS and for a large conductance (135–200pS) channel (39). Nucleoside diphosphates (NDP) are required for the opening of the small/medium conductance channel, and they are therefore often referred to as K$_{NDP}$ channels. The opening of vascular K$_{NDP}$ channels is stimulated by metabolic impairment, including intracellular ATP depletion, hypoxia, and metabolic inhibition (40–42). Pharmacologically, their opening is promoted by 'classical' K$_{ATP}$ channel openers such as levcromakalim, pinacidil, nicorandil, and diazoxide (41,43–48) and inhibited by K$_{ATP}$ channel blockers such as glibenclamide (41,42,45).

K$_{ATP}$ channels are also expressed in the vascular endothelium. In most studies, membrane hyperpolarization of endothelial cells occurs in response to K$_{ATP}$ channel openers such as levcromakalim, rimakalim, pinacidil, minoxidil, and diazoxide (49–53). Moreover, a glibenclamide-sensitive K$_{ATP}$ channel current can be elicited in whole-cell patch clamp experiments with freshly isolated cerebral microvascular and rat aortic endothelial cells (49,53,54). It is possible that endothelial K$_{ATP}$ channels are constitutively active since glibenclamide inhibits basal membrane currents in bovine pulmonary endothelial cells (55). In isolated inside-out patches, the K$_{ATP}$ channel may have a unitary conductance of about 40pS (54), although another study described the presence of two types of K$_{ATP}$ channels with unitary conductances of 25 and 150pS (49). Endothelial K$_{ATP}$ channels may help to regulate blood flow (56,57), possibly by regulating the release of vasoactive compounds such as nitric oxide and endothelin-1 (58,59). Thus, endothelial K$_{ATP}$ channels may be an important link between the metabolic status and coronary function.

Molecular studies
Vascular smooth muscle expresses high levels of the K$_{ATP}$ channel subunits Kir6.1 and SUR2B, with little or no expression of SUR1 or SUR2A (60–63). Credence of the premise that these two subunits are molecular components of smooth muscle K$_{ATP}$ channels comes from the arguments that 1) overexpression of these subunits leads to the formation of channels with properties similar to those of smooth muscle K$_{NDP}$ channels (64) and that 2) genetic deletion of either Kir6.1$^{-/-}$ or SUR2$^{-/-}$ in mice abolish K$_{ATP}$ channel activity in aortic smooth muscle myocytes (65,66). The endothelial K$_{ATP}$ channel is not fully characterized and published reports show the expression of Kir6.1, Kir6.2, and SUR2B in the endothelium (52,53,67). Transgenic overexpression of Kir6 dominant-negative subunits in the endothelium lead to

impaired coronary artery function, elevated blood pressure, and defects in ET1 release (59). A permissive role for Kir6.2 is demonstrated by the finding that pulmonary artery endothelial cells isolated from Kir6.2$^{-/-}$ mice have an impaired response in membrane potential changes and reactive oxygen species (ROS) generation associated with shear stress (68).

Effects of aging on vascular K$_{ATP}$ channels

Natural aging is associated with structural and functional changes in blood vessels. These changes may contribute to the development of vascular diseases, such as coronary artery disease, heart failure, essential hypertension, and postural hypotension. Structural changes include the development of vascular stiffness and deficits in compliance. Functional changes take place both in the vascular smooth muscle and in the endothelium (69). The functional defects appear to be associated with (or caused by) deficits in intracellular Ca^{2+} homeostasis, and process that regulate intracellular Ca^{2+} homeostasis, such as the activity of the Na^+/K^+-ATPase (69). Little is known about how aging affects vascular smooth muscle or endothelial K$_{ATP}$ channels. In brain stem vessels, the dilator responses of the basilar artery branches (but not of the main artery itself) in response to K$_{ATP}$ channel openers levcromakalim or Y-26763 were diminished in aged (24–26 months) Sprague-Dawley rats (70). Similarly, in intact aortic segments from 3-year-old rabbits, the vasodilator response induced by cromakalim was significantly impaired (71). In contrast, the intrinsic activity of the K$_{ATP}$ channel to PKA or to the K$_{ATP}$ channel opener, nicorandil, appears to be largely unaffected (70,72). There is evidence that impaired PKA signaling may attenuate K$_{ATP}$ channel opening in cultured rat aortic vascular smooth muscle cells (72), which would translate to impaired PKA-mediated vasodilatation and blood pressure regulation if this results holds in vivo. Indeed, isoproterenol-induced hyperpolarization of isolated mesenteric arteries was found to be impaired in aged rats (73). In summary, there are very few studies that investigated how the aging process affects vascular and endothelial K$_{ATP}$ channels. There is evidence that endothelium-dependent hyperpolarization (produced by acetylcholine) is markedly impaired in aged Wistar-Kyoto (WKY) rats (74). Overall, based on the literature, it is likely that the contribution of endothelial and smooth muscle K$_{ATP}$ channels to vasoreactivity is strongly impaired in the aged vascular system.

Mitochondrial K$_{ATP}$ channels
The native channel
In the heart, mitochondrial oxidation is an important fuel under normal conditions and the role of mitochondria to heart function cannot be underestimated. There is strong evidence for a type of a K$_{ATP}$ channel in the inner mitochondrial membrane, which differs in many respects from the cardiomyocyte or vascular K$_{ATP}$ channels. The

mitochondrial K$_{ATP}$ channel (mito-K$_{ATP}$ channel) has first been identified in the inside out with patch clamp approaches in giant mitoplasts from rat liver (75). Opening of the channel was inhibited by millimolar concentrations of ATP (as opposed to the micromolar ATP concentrations needed to block cardiac or vascular K$_{ATP}$ channels). Moreover, the single channel conductance of the mito-K$_{ATP}$ channel was reported to be very small (about 10pS) as opposed to the 30–85pS unitary conductances of other plasma/sarcolemmal K$_{ATP}$ channels (12). There have been further patch clamp studies of mito-K$_{ATP}$ channels (76–78), but data are not consistent, with reported unitary conductances ranging from 24 to 220pS. Moreover, not all studies were successful in finding evidence for K$_{ATP}$ channels in mitochondria with patch clamp techniques (79–83). Many studies do not directly measure mito-K$_{ATP}$ channels with electrophysiological recordings, but rely on surrogate methods, such as K^+, $^{86}Rb^+$ or Tl^+ flux assays of reconstituted channels in liposomes or isolated mitochondrial preparations (84–88). In these studies, MgATP more efficiently blocks the mito-K$_{ATP}$ channel. The mito-K$_{ATP}$ channel has an overlapping pharmacology with other types of K$_{ATP}$ channels, being activated by compounds such as pinacidil, cromakalim, and diazoxide, and blocked by tolbutamide, glibenclamide, and 5-hydroxydecanoate (5-HD) (12,89).

Molecular subunits and knockout approaches
The molecular composition of mito-K$_{ATP}$ channels is debated and is not well defined. Initially, the Kir6.1 subunit was proposed to be a candidate (90), but not all subsequent studies are in agreement (12). The observation that mitochondrial function and mito-K$_{ATP}$ channel activity are unaffected in Kir6.1$^{-/-}$ or Kir6.2$^{-/-}$ mice (91,92) argues against the premise that these subunits are essential components of the mitochondrial channel. Current data suggest instead a potential role for a Kir1.1 splice variant (93) and/or a short splice variant of the SUR2 subunit (94). To date, no genetic knockout approaches have been confirmed the molecular identity of the mito-K$_{ATP}$ channel.

Changes in mito-K$_{ATP}$ channels with advanced age
A decline in mitochondrial morphology, density and function occurs with advanced aging, cell senescence and cell death. This is observed in a variety of tissues and organs, including the heart. The decline in mitochondria function may potentially directly contribute to the aging process (95), although some would argue that the mitochondrial theory of aging is overestimated (96). Regardless, the question remains of how the mito-K$_{ATP}$ channel is affected by aging and whether any potential changes may contribute to a deficit in mitochondrial capacity. Unfortunately, this question is not resolved in the prevailing literature. There are indications that the mitochondrial potassium cycle is impaired in 24-month-old

Wistar male rats and that the intra-mitochondrial K$^+$ concentration is decreased (97). Some studies show that diazoxide has protective effects on mitochondrial function during advanced age (98,99). However, diazoxide is an effective inhibitor of succinate dehydrogenase and complex II respiration (100–103) and it is not entirely clear whether the protective effects of diazoxide result from an action on mito-K$_{ATP}$ channels or the inherent protective nature of complex II inhibition (104,105). Patch clamp studies are needed to examine whether the mito-K$_{ATP}$ channel is affected by advanced age and genetic studies are also needed (once the subunit composition has been established) to determine how mito-K$_{ATP}$ channels contribute to mitochondrial function during advanced age.

Possible roles for K$_{ATP}$ channels in the aging-related physiological and pathophysiological processes

We will briefly review the possibility that K$_{ATP}$ channels may be involved in physiological and pathophysiological processes during advanced aging. It should be noted that the literature is scant and some sections are somewhat speculative.

Exercise

During advanced aging, the ability of the cardiovascular system to respond to stress is significantly decreased. This includes physiological stressors such as exercise, which results in a decreased maximum cardiac output and impaired reserve capacity of the aging heart (106). The decline in physical endurance is associated with a decrease in cardiac K$_{ATP}$ channel currents (see 'Effects of aging on the ventricular K$_{ATP}$ channel'). Interestingly, transgenic overexpression of the K$_{ATP}$ channel subunit, SUR2A, in mice is associated with improved physical endurance (107), suggestive of a permissive role for K$_{ATP}$ channels. In the latter study, the SUR2A subunit was expressed under the control of a strong and ubiquitous CMV promoter, which makes it difficult to assign the protective role to K$_{ATP}$ channels in the heart. Likewise, global knockout of the Kir6.2 K$_{ATP}$ channel subunit leads to reduced exercise tolerance in mice (108). Since cardiac-specific overexpression of a dominant-negative K$_{ATP}$ channel subunit in mice also results in a phenotype of reduced exercise tolerance (109), it is very likely that cardiac K$_{ATP}$ channels are in fact involved. Studies in rats also support the concept that cardioprotection afforded by chronic exercise is mediated by sarcolemmal K$_{ATP}$ channels (110,111). In humans, the Kir6.2 E23K variant was found to be overrepresented in heart failure and to be associated with impaired exercise stress response (112). Interestingly, upregulation of cardiac K$_{ATP}$ channels occurs vary rapidly with exercise, suggesting the possibility that the beneficial effects of exercise in advanced aging

might be, at least in part, due to upregulated cardiac K$_{ATP}$ channel currents.

Ischemia/reperfusion injury

In an aging society, where advanced age independently adds to the already high cardiovascular risk, our nation faces a health and financial problem in the years to come. Not only is there an inherent decline in cardiovascular function in the aged heart, but the aged heart becomes much more vulnerable to superimposed stresses such as cardiac ischemia (113,114). Thus, when ischemia is superimposed on the already impaired aged heart, enhanced susceptibility to ischemia/reperfusion (I/R) injury occurs (115–118). In general, K$_{ATP}$ channels (both the sarcolemmal and mitochondrial subtypes) are considered to have protective roles during cardiac ischemia (12). The decline in K$_{ATP}$ channel function and regulation during advanced aging therefore leads to the expectation that the increased susceptibility to ischemic stress might (at least in part) be due to the K$_{ATP}$ channel deficit. The K$_{ATP}$ channel opener, nicorandil, however, remains highly cardioprotective in aged rats (119,120). Nicodandil is a nicotinamide derivative with a nitrate group and it is unclear to what extent the protective effects of this compound are related to blood flow improvement independent of K$_{ATP}$ channels. Another K$_{ATP}$ channel opener, minoxidil, was found to induce necrosis in aged (but not young) rat hearts (121). The K$_{ATP}$ channel opener, diazoxide, is very effective against cardiac ischemic injury (12,89), but loses its protective effects against cardiac I/R in the aged (>32 months) rabbit (122).

Ischemic and pharmacological preconditioning

Not only is the decline in innate cardiovascular function with advanced age associated with increased injury resulting from I/R, but the endogenous protection mechanisms of the heart against I/R injury is also greatly diminished (117,123–126). The best known protective mechanism is that of ischemic preconditioning (IPC), in which short bursts of ischemia that precedes a longer (index) ischemic event paradoxically protects the heart from injury, for example by reducing the amount of infarcted tissue (127). K$_{ATP}$ channel blockers, such as glibenclamide and 5-hydroxydecanoic acid (5-HD), effectively reduces the protective effects of IPC. Furthermore, pretreatment of a heart with a variety of K$_{ATP}$ channel openers, including cromakalim, aprikalim, bimakalim, diazoxide, nicorandil, and pinacidil, mimics the cardioprotective effects of IPC (12), which led to the premise that K$_{ATP}$ channels are involved in the protective effects of IPC. Consistent with a decline in K$_{ATP}$ channel, the protective effects of IPC during advanced age is significantly reduced (123–125). This is also observed in humans. The protective effects of preconditioning is absent in elderly patients undergoing coronary angioplasty; an

effect that can be overcome by the K_{ATP} channel opener nicorandil (128).

It should be noted that IPC has a complex mechanism and intracellular signaling, notably by PKC, has an essential role (129). Thus, IPC can also be mimicked by receptors (e.g. by adenosine or α-adrenoceptors) that signal though PKC. This form of precondition is often referred to as pharmacological preconditioning (PPC). Interestingly, pretreatment of cardiomyocytes with the α-adrenoceptor agonist, phenylephrine, not only is protective against 'ischemic' injury, but also upregulates K_{ATP} channel current density, also suggesting a key role for K_{ATP} channels in this form of cardioprotection (130). In support, we recently demonstrated that K_{ATP} channels are essential to mediate the infarct-limiting effects of IPC (since it was absent on mice that lack cardiac K_{ATP} channels). Moreover, ischemia caused internalization of the protective K_{ATP} channel; an effect that was prevented by IPC and was mediated by PKC (131). Interestingly, the protective effects of PPC with adenosine is lost in aged (16–18 months) mice, whereas the K_{ATP} channel opener diazoxide reduced ischemic damage in both young and old hearts (132). This result suggests an uncoupling of the intracellular pathways underlying IPC during advanced age, but mechanistic insights await further research.

Arrhythmias

Cardiac arrhythmias is a serious health concern, with atrial fibrillation (AF) the most common abnormal heart rhythm in the aged population (133,134). The molecular mechanisms of AF and ventricular tachycardia (VT) are diverse (135), with potential roles for altered ion channel activities and impaired intracellular Ca^{2+} handling (136). K_{ATP} channels have a potential role in the genesis of arrhythmias, as demonstrated by the observation of a predisposition to adrenergic AF originating from the vein of Marshall in a patient with a missense mutation (Thr1547Ile) in the ABCC9 gene (which codes for the SUR2 K_{ATP} channel subunit) (137). Moreover, a KCNJ8 mutation was also found to be associated with early repolarization and AF (138) and the K_{ATP} channel current density was found to be decreased during chronic human AF (139). A curious result was observed in aged (about 24 months old) rat hearts, in that glycolytic inhibition was found to cause spontaneous ventricular fibrillation in the aged (but not young) hearts, which was suppressed by the K_{ATP} channel blocker glibenclamide (140). It is unclear to what extent this result relates to the regulation of K_{ATP} channels by glycolytically derived ATP (33,141). The specific role of K_{ATP} channels during arrhythmogenesis in the aging heart, however, has not been formally investigated.

Conclusion and future directions

The literature is clear in that the aging cardiovascular system undergoes an innate decline in function and
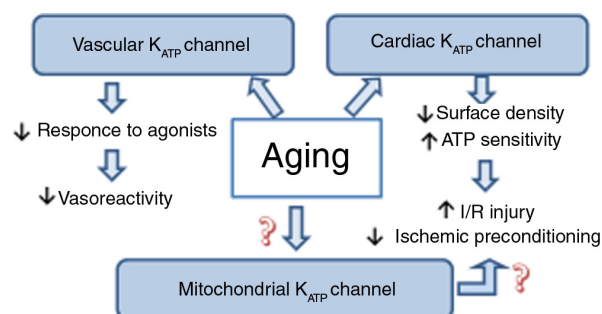

Fig. 1. Several classes of K_{ATP} channels in the cardiovascular system are impaired during innate aging, including K_{ATP} channels in the heart muscle, in the vasculature (smooth muscle and possibly the endothelium) and those in the mitochondrial inner membrane. Together, the functional deficit on these K_{ATP} channels may account for alterations in blood flow and impaired responses of the cardiovascular system to superimposed stresses such as ischemia/reperfusion, and loss of endogenous protection mechanisms of the heart (such as ischemic preconditioning).

metabolism, and becomes less adaptive to superimposed stresses, such as exercise and cardiac ischemia. It is also clear that the K_{ATP} channel is diminished (and possibly dysregulated) during advanced age. The protective role of the K_{ATP} channel is therefore expected to be diminished during advanced age, a premise that is supported by the literature. Roles appear to exist for the contribution of several types of K_{ATP} channels, including those in the heart, vasculature, and mitochondria (Fig. 1). Many questions, however, remain unanswered, and future research is warranted to determine the cellular and molecular mechanisms that cause K_{ATP} channel dysfunction. Systematic studies are needed to examine transcriptional profiles of K_{ATP} channel subunits and their regulation by transcription factors and histone modification. Post-transcriptional regulation of the K_{ATP} channel subunits by processes such as phosphorylation and ubiquitination must be closely examined. The regulation of channel function during aging, for example by intracellular metabolism (which is known to be pliable during aging) and ROS must also be defined. These studies may reveal targets for therapy and intervention. Attractive pathways to explore are those known to be beneficial during aging, such as combating changes in cellular NAD^+ levels (142), caloric restriction, resveratrol, and melatonin (143).

Conflict of interest and funding

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