CONTRIBUTION OF POTASSIUM CHANNELS TO MYOGENIC RESPONSE IN SKELETAL MUSCLE ARTERIOLES: EFFECTS OF AGE AND FIBER TYPE

A Thesis

by

SE JEONG KIM

Submitted to the Office of Graduate Studies of
Texas A&M University
in partial fulfillment of the requirements for the degree of

MASTER OF SCIENCE

August 2005

Major Subject: Kinesiology

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Approved by:

Chair of Committee, Judy Muller-Delp
Committee Members, Michael Delp
Emily Wilson
Head of Department, Steve M. Dorman

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ABSTRACT

Contribution of Potassium Channels to Myogenic Response

in Skeletal Muscle Arterioles: Effects of Age and Fiber Type. (August 2005)

Se Jeong Kim, B.Ed., Kyungsung University;

M.Ed., Yonsei University

Chair of Advisory Committee: Dr. Judy Muller-Delp

In isolated skeletal muscle arterioles, increasing transmural pressure causes an increase in constriction. This active myogenic response varies with age and fiber type. Increased transmural pressure activates both Ca^{2+}-activated (K_{Ca}) potassium channels and voltage-dependent (K_v) potassium channels; these channels have a role in the negative-feedback pathways that modulate depolarization and myogenic constriction. We tested the hypothesis that increased K_{Ca} channel and K_v channel activity contribute to reduced myogenic responsiveness in skeletal muscle arterioles of aged rats. 1A arterioles were isolated from soleus, an oxidative muscle, and superficial gastrocnemius, a glycolytic muscle, of young (4 mos) and aged (24 mos) Fischer 344 rats. Myogenic responses were assessed by increasing intraluminal pressure (0-140 cm H_2O) in increments of 20cm H_2O. Vasoconstrictor response were determined in response to increasing concentrations of the K_{Ca} channel blocker, charybdotoxin (CTX; 10^{-10} to 10^{-7} M) and the K_v channel blocker, 4-Aminopyridine (4-AP; 10^{-5} to 10^{-2} M). To determine the role of potassium channels in modulating the myogenic response, cannulated arterioles from soleus and gastrocnemius were incubated with CTX (50 nM) and 4-AP (5mM) for 15 minutes prior to evaluation of the myogenic response. Increased K_v channel activity contributes to reduced myogenic

constriction in soleus and gastrocnemius muscle arterioles from aged rats. In soleus muscle arterioles, K_{Ca} channel activity opposes myogenic tone in young but not old rats. In gastrocnemius muscle arterioles, treatment with CTX did not eliminate age-related differences in the myogenic response, and the K_{Ca} channel contribution to myogenic tone was, in fact, greater arterioles from young as compared to old rats. K_v channels contribute to greater myogenic constriction in soleus arterioles, K_{Ca} channels appear to be more active in gastrocnemius muscle arterioles as compared to soleus muscle arterioles. Therefore K_v and K_{Ca} channels are tonically active in skeletal muscle arterioles, contributing to a hyperpolarizing force that opposes myogenic constriction. Furthermore, increased K_v channel activity contributes to the age-related reduction of myogenic constriction in soleus and gastrocnemius muscle arterioles.

ACKNOWLEDGMENTS

This thesis was possible only with the help and support of others for which I can never take credit. I would like to express my sincere gratitude to all those who have given the most profound influence to me in making this thesis possible.

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On my personal note, I appreciate to my parents who have given continuous support and encouragement for my life even still today. I thank my daughter, Minji, who has done everything with me and I also feel sorry about her insufficient care during her childhood. I would like to express a great thank you to my husband. Without their help and patience, it was never possible that I received this achievement.

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INTRODUCTION

Aging results in various physiological alterations in the structure and function of the cardiovascular system (21), and is a major risk factor for cardiovascular disease (61). The strength and speed of contraction of cardiac and vascular smooth muscle decline with age. This attenuated contraction can influence cardiac function and vascular responsiveness (20). The effect of aging on smooth muscle of resistance vessels has been studied in perfused renal (29), coronary (27), and hind quarter vascular beds (26). These studies indicate that contractile responsiveness of vascular smooth muscle changes with age, in part due to alterations in excitation-contraction coupling (25).

Peripheral vascular resistance in response to head-up tilt and orthostatic challenges is altered in the aged (60). Furthermore, age-related changes in the central and peripheral circulation with aging can influence compliance in arteries and arterioles which play an important role in control of total peripheral resistance (6).

In isolated skeletal muscle vasculature, increasing perfusion pressure causes a gradual increase in vascular resistance (39) these adjustments contribute to maintenance of fairly constant flow and capillary hydrostatic pressure over a range of arterial pressures (37). This ability to adjust resistance over a range of pressures is defined as myogenic autoregulation. In isolated blood vessels the myogenic response is defined as the ability of vascular smooth muscle to constrict in response to an increase in transmural pressure and to dilate as intravascular pressure is decreased (14). Therefore, the myogenic response is a major physiological factor in determining arterial blood pressure (21). Aging has been shown to impair the magnitude of the myogenic response in mesenteric

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(30) and skeletal muscle arterioles (5). Our previous study suggests that age-related alterations of contractile mechanisms of vascular smooth muscle contribute to reduced myogenic reactivity in skeletal muscle resistance arterioles (50).

Ion channels in the plasma membrane of vascular smooth muscle cells of resistance arteries and arterioles are important in the control of vascular tone (35). Movement of ions through channels with specific and selective ionic permeabilities modulates contraction of skeletal muscle (56). Contraction in vascular smooth muscle depends on an increase in intracellular Ca^{2+} (13). Membrane potential is the main variable that regulates Ca^{2+} influx through voltage-gated Ca^{2+} channels (VGCC), in turn modulating release of Ca^{2+} from sarcoplasmic recticulum (35). Thus, a tight relationship exists between membrane potential, Ca^{2+} influx, intracellular calcium concentration, and maintenance of force in vascular smooth muscle (13). Additionally, K^+ channels influence ion conductance in vascular smooth muscle cells and contribute to determination of membrane potential, activation of VGCC, and vascular tone (35). Specifically, vascular smooth muscle cells have voltage-gated (K_v) and high-conductance, Ca^{2+}-activated K^+ channels (K_{Ca}) that contribute to control of membrane potential and which exert a negative effect on contractile responses (52). During myogenic stimulation of vascular smooth muscle, activation of K_{Ca} channels and K_v channels results in diffusion of K^+ out of the cells, leading to membrane hyperpolarization (11). Therefore, K^+ channels act as a negative feedback mechanism modulating the development of myogenic tone in resistance arterioles.

Our previous work indicates that myogenic contraction is impaired with age in skeletal muscle arteriole; however, the cellular mechanisms that underlie this reduction of

myogenic responsiveness have not been identified. Therefore, the goal of this work was to determine the role of K_{Ca} and K_v channels in regulation of myogenic tone in resistance arterioles from the soleus and gastrocnemius muscles of young and old Fischer 344 rats. We hypothesized that increased activity of potassium channels contributes to reduced myogenic responsiveness in skeletal muscle arterioles from aged Fischer 344 rats.

Myogenic Response

Constriction of blood vessels in response to changes in intravascular pressure relies on intrinsic mechanisms of vascular smooth muscle cells (62). Increased transmural pressure causes resistance vessels to constrict and decreased transmural pressure causes dilation (24). This myogenic mechanism responds to acute changes in transmural pressure (44), and the myogenic response of small resistance vessels is important to local control of blood flow in the microcirculation and maintenance of capillary transmural pressure (49). In human skeletal muscle, myogenic constriction helps prevent severe edema in the leg during upright exercise (45). Thus, myogenic autoregulation contributes to regulation of arterial blood pressure during important physiological adjustments, i.e., orthostasis and changes in activity (21). Importantly, this inherent ability of vascular smooth muscle can modulate vascular resistance rapidly over a range of arterial pressures (44).

The cellular mechanisms that are responsible for the myogenic response are not well defined (32); however, several studies suggest that electrophysiological and ionic mechanisms are important to the myogenic response (48). Acute pressure changes alter both membrane potential of smooth muscle and the diameter of resistance vessels (52).

Transmural pressure can control membrane ionic conductance (15), and subsequently activate contractile proteins through activation of intracellular second messengers (32). Voltage-gated calcium channels in smooth muscle cell are critical to myogenic contraction (31). Both voltage-gated Ca^{2+} channel blocker, nimodipine, and removal of extracellular Ca^{2+} cause dilation of arteries at low or high pressures (1). Thus, the myogenic response is modulated by membrane depolarization that occurs with an increase in transmural pressure and also by membrane hyperpolarization that accompanies relaxation upon reduction of intravascular pressure (38). In addition, release of intracellular Ca^{2+} (23) and activation of Ca^{2+} sensitive contractile proteins influence myogenic activity (33). Thus, myogenic autoregulation occurs, in part, through regulation of Ca^{2+} homeostasis by steady-state Ca^{2+} influx through Ca^{2+} channels and modulation of Ca^{2+} release from sarcoplasmic reticulum (4). Furthermore, myogenic constriction clearly depends upon activation of voltage dependent Ca^{2+} channels, which is tightly coupled to myogenic depolarization (53).

Potassium Channels and Myogenic Tone

K^+ channel activity is also critical to regulation of arterial diameter and regulation of myogenic tone (52). K^+ channels function as a dynamic mechanism to lower arterial blood pressure through membrane hyperpolarization of vascular smooth muscle (52). Specifically, K_{Ca} channels and K_v channels act as negative-feedback pathways in vascular smooth muscle to limit depolarization and constriction (41). These channels function in regulation of vascular smooth muscle membrane potential, thus, regulating arterial tone and, hence, arterial diameter (52). Opening of K^+ channels leads to an outward flux of K^+

ion, hyperpolarization of smooth muscle membrane potential, decreasing the open probability of vascular smooth muscle voltage-dependent Ca^{2+} channels, and consequently, decreasing Ca^{2+} entry leads, which leads to vasodilation (52).

K^+ channels play an important role in regulation of peripheral vascular resistance through prevention of overconstriction in vascular smooth muscle. These channels contribute to control of membrane potential and arterial diameter in small resistance vessels (22). The most prevalent K^+ channels in vascular smooth muscle are K_v channels and K_{Ca} channels (42). Activation or inhibition of K^+ channels is associated with changes in membrane potential, isometric force, and diameter of pressurized arteries (52). The variety of K^+ channels in different vascular beds that contribute to vascular relaxation reflects the multiplicity and complexity of the signaling mechanisms involved in the regulation of vascular tone (42). In this work, we have specifically investigated the contribution of K_v and K_{Ca} channels to regulation of myogenic tone in resistance arterioles from soleus and gastrocnemius muscles from young and aged rats.

K_{Ca} Channels and Vascular Tone

K_{Ca} channels play a significant role in the modulation of small artery tone and fine-tuning of agonist- and pressure-induced constriction in vascular smooth muscle cells (36). Increase of intracellular Ca^{2+} increases vascular tone, and also increases the open probability of K_{Ca} channels in pressurized arteries (7). Thus, large positive increases in membrane potential activate K_{Ca} channels. K_{Ca} channel activation produces smooth muscle membrane hyperpolarization, which results in vasodilation (8). Thus, K_{Ca} channels acts as a braking mechanism for vascular smooth muscle constriction,

preventing vasospasm from a prolonged constriction accompanied by an increase of intracellular calcium concentration (58).

Myogenic tone is associated with both Ca^{2+} influx through membrane Ca^{+} channels (31) and release of Ca^{2+} from stores in the sarcoplasmic recticulum (53). Brenner et al., (10) suggested that deletion of the gene for the β_1-subunit of K_{Ca} channels resulted in reduction of Ca^{2+} sensitivity of K_{Ca} channels in arterial smooth muscle. They showed that when Ca^{2+} and K_{Ca} channel activity were uncoupled by this manipulation, arterial tone and blood pressure increased (10). Similarly, myogenic tone of cerebral arteries is increased by charybdotoxin (CTX), a K_{Ca} channel inhibitor (63). At physiological levels of pressure, pharmacological blockade with CTX causes vascular smooth muscle depolarization and contraction (63). Specific blockers of K_{Ca} channels such as charybdotoxin and iberiotoxin provide strong evidence of the role of K_{Ca} channels in modulation of vascular tone in intact tissues (28). K_{Ca} channels can also be inhibited by reducing calcium entry through VGCC with calcium channel antagonists (57). Thus, increasing transmural pressure induces membrane depolarization and myogenic tone (63), primarily through Ca^{2+} entry and release of intracellular Ca^{2+}; however, myogenic tone is also influenced by Ca^{2+} activated K_{Ca} channels (16).

K_v Channels and Vascular Tone

Voltage-gated K^{+} channels play a substantial role in regulate of arterial tone by modulating the membrane potential of vascular smooth muscle cells (2). These channels open with depolarization of membrane potential. Upon depolarization, K^{+} efflux through these channels increases (34). The increase in K^{+} efflux results in membrane

hyperpolarization and reduces tone (5). Therefore, activity of K_v channels during pressurization or in response to vasoconstrictor agents may offset membrane depolarization (52) limiting myogenic and agonist constriction.

There is evidence to support the contribution of K_v channel activity to maintenance of vascular smooth muscle membrane potential and tone in pressurized arteries (12). For instance, 4-aminopyridine (4-AP), a specific inhibitor of K_v channels, causes marked vasoconstriction during increases of coronary perfusion pressure (36). 4-AP-induced membrane depolarization and vasoconstriction are not changed by blockade of K_{ATP} channels, K_{ir} channels, calcium channels, K_{Ca} channels, denudation of the endothelium, or a variety of receptor blockers (40). Therefore, 4-AP-induced constrictions are not mediated by the release of factors from the endothelium or by variety of agonists (40). Furthermore, blockade of K_v channels with 4-AP significantly increases vasoconstriction at pressures greater than 30 mmHg (41) and 4-AP induces significantly larger constriction at high pressure, when compared with that induced at low pressure (1).

K_v channels exhibit exponential increases in open probability upon depolarization and likely serve an important role in the repolarization of vascular smooth muscle (53). K_v channel blockers depolarize vascular smooth muscle cells in pressurized arterioles and augment myogenic tone (34). Thus, K_v channels are important modulators of vascular smooth muscle membrane potential in pressurized arteries and contribute importantly to regulation of myogenic tone. According, we specifically investigated the role of these channels in regulation of myogenic tone in resistance arterioles from soleus and gastrocnemius from young and aged Fisher 344 rats.

METHODS

Animal Model

Young (4 mos) and old (24 mos) male Fischer 344 rats were used as a model for this study. These rats were chosen because previous aging studies have shown that cardiovascular function decreases in these rats with age in the absence of atherosclerosis or hypertension (43). Animals were cared for at the LARR (Laboratory Animal Resources and Research) facility at Texas A&M University in accordance with NIH and ULACC (University Laboratory Care Committee) standards. Arterioles were isolated from skeletal muscle microvasculature. Sepcifically, arterioles were isolated from the soleus, a predominantly slow-twitch muscle, and the superficial portion of the gastrocnemius, a predominantly fast-twitch muscle (19).

Microvessel Preparation

Rats were anesthetized with sodium pentobarbital (100mg/kg). The gastrocnemius-plantaris-soleus muscle group was carefully dissected free from both hindlimbs and placed in a cold, filtered physiological saline solution containing 1% albumin (50). 1A resistance arterioles were isolated and dissected free from the soleus and the superficial portion of the gastrocnemius muscle. The arterioles (100-200 μm inner diameter) were transferred to a chamber containing physiological saline-albumin solution (PSS) at pH 7.4, and equilibrated with room air. Arterioles were cannulated with micropipettes of matched tip resistance and secured with nylon suture. The chamber containing the arteriole was then placed on the stage of an inverted microscope, coupled to a video camera, TV monitor, and video caliper device for measurement of changes in

arteriolar diameter. The micropipettes used to cannulate the arterioles were filled with the PSS and each micropipette was connected to a pressure transducer and a hydrostatic pressure reservoir. Adjustment of the height of the reservoir allowed for manipulation of transmural pressure. If pressurization indicated that no leaks were present, arterioles were pressurized to 70cm H_2O, warmed gradually to 37°C, and allowed to equilibrate for 60 minutes.

Experimental Procedures

Myogenic Response:

To determine the response of smooth muscle to increases in transmural pressure, soleus and gastrocnemius muscle arterioles of young and old Fischer rats were exposed to pressure steps of 20cm H_2O from 0 to 140 cm H_2O. Vessel diameter was monitored for 5 minutes following each pressure increase.

Myogenic Response in the Presence of Potassium Channel Blockade:

To determine the role of K_{Ca} and K_V channel in modulation of myogenic tone in soleus and gastrocnemius muscles arterioles from young and old Fischer rats, myogenic constriction was evaluated in response to elevations of transmular pressure from 0 to 140 cm H_2O in the presence of either CTX (50nM) or 4-AP (5mM).

Vasoconstrictor Responsiveness to Potassium Channel Blockade:

To determine sensitivity and maximal responsiveness of soleus and gastrocnemius muscle arterioles to K_V and K_{Ca} channel inhibitors, concentration-response curves were

determined for CTX and 4-AP. Diameter responses were recorded as arterioles were exposed to increasing concentrations of CTX (10^{-10} to 10^{-7} M) or 4-AP (10^{-5} to 10^{-2} M).

Data Presentation and Statistical Analysis

Responses were recorded as actual inner diameters and expressed as spontaneous tone (in %), normalized diameter, and constriction (in %). These values were derived using the following formulas:

$$\text{Spontaneous tone (\%)} = (ID_{max} - ID_b)/ID_{max} \text{ X } 100$$

ID_{max} is the maximal inner diameter recorded at a pressure of 70 cm H_2O and ID_b is the steady-state baseline diameter.

$$\text{Normarized diameter} = (ID_s/ID_{max})$$

ID_s is steady-state diameter measured after each incremental pressure change. Diameter is normalized to account for differences in vessel size between young and old animals.

$$\text{Constriction (\%)} = (ID_b - ID_s)/ID_b \text{ X } 100$$

ID_b is the initial diameter recorded immediately before the addition of the vasoconstrictor agonist and ID_s is the steady-state diameter measured after each dose of the drug.

Myogenic response and concentration response curves were compared by two way repeated analysis of variance (ANOVA) in order to detect differences between (young vs. old) and within (pressure or drug) groups. Maximal response to CTX and 4-AP were compared by t-test. In all experiments, n indicated the number of animals studied.

RESULTS

Animals

Body weight was significantly greater with old age. Young rats weighed 323 ± 7 g and aged rats weighed 428 ± 6 g. Heart weight was also significantly greater in aged rats. Heart weight of young rats was 0.75 ± 0.02 g and heart weight of young rats was 1.02 ± 0.02 g.

Characteristics of Isolated Vessels

Vessel characteristics are shown in Table 1. Maximal diameters of arterioles from soleus muscle ranged from 78μm to 165μm in young rats and from 91μm to 177μm in old rats, with no difference between young and old groups. Maximal diameter of arterioles from the gastrocnemius muscle of young animals ranged from 75μm to 189μm and in aged animals from 117μm to 213μm; maximal diameter in old rats was larger ($p = 0.0212$) than that in young animals. The level of development of spontaneous tone at 70 cmH_2O varied with age and muscle (Table 1). Tone development in soleus muscle arterioles from young rats was greater than that in soleus muscle arterioles from old rats ($p = 0.0659$). Arterioles from the gastrocnemius muscle of young rats developed similar tone as those from aged animals. However, arterioles from the soleus muscle showed greater spontaneous tone than arterioles from gastrocnemius muscle in both young and old rats ($p < 0.01$).

Table 1. Characteristics of First-order Arterioles from Soleus Muscle and Gastrocnemius Muscle

	Soleus		Gastrocnemius	
	Young	Old	Young	Old
Maximal Diameter, μm	n = 21 118 ± 6	n = 18 116 ± 5	n = 21 159 ± 6^{+}	n = 17 179 ± 6** $^{+}$
Spontaneous tone, %	n = 21 53 ± 4	n = 18 44 ± 3*	n = 21 37 ± 3^{+}	n = 17 31 ± 2^{+}

Value are mean ± SE; n = number. * significant difference between young and old groups ($p < 0.1$); ** significant difference between young and old groups ($p < 0.05$); $^{+}$ significant difference between soleus and gastrocnemius muscle arterioles ($p < 0.01$).

Myogenic Responses

Figure 1 illustrates pressure-diameter relationships as intraluminal pressure was increased stepwise from 0 to 140 cm H_2O. Arterioles from both the soleus and gastrocnemius muscles of young and old rats displayed myogenic constriction. In addition, myogenic responsiveness of arterioles from both soleus and gastrocnemius muscle from aged rats were significantly less than that of arterioles from young rats. Arterioles from the soleus muscle displayed significantly greater myogenic constriction than arterioles from the gastrocnemius in both young and old animals.

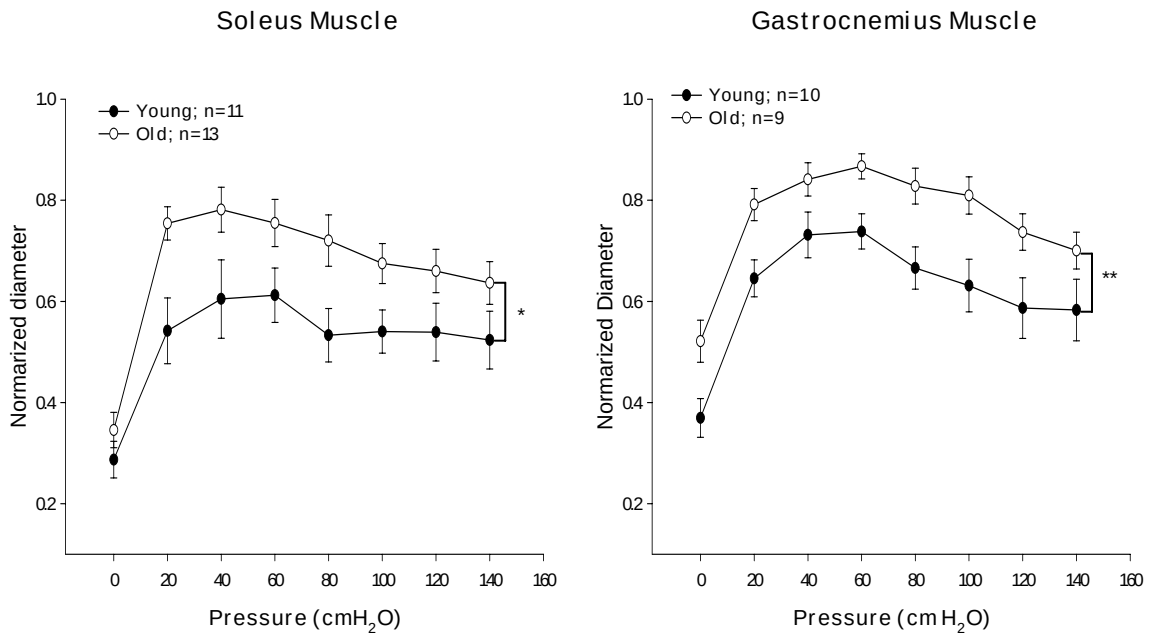

Figure 1. Myogenic responses to increasing intraluminal pressure in soleus and gastrocnemius muscle arterioles from young and old rats. Data are presented as means ± SE. Myogenic responses of soleus (*$p < 0.05$) and gastrocnemius (**$p < 0.01$) muscle arterioles differed significantly between young and old groups.

Contribution of K_v Channels to Myogenic Response

Figure 2 shows myogenic responses in the presence of K_v channel blockade with 4-AP. 4-AP increased myogenic constriction to a greater degree in arterioles from old rats. In the presence of 4-AP, age-related differences in the myogenic responses were eliminated. Figure 3 illustrates the contribution of K_v channels to the myogenic response in arterioles from young and old rats. In soleus muscle arterioles, 4-AP enhancement of myogenic constriction was greater in old rats as compared to young rats. In gastrocnemius muscle, 4-AP significantly increased the myogenic response in arterioles from old but not young rats. Therefore, the counteractive contribution of K_v channels to myogenic constriction is increased in skeletal muscle arterioles from old rats.

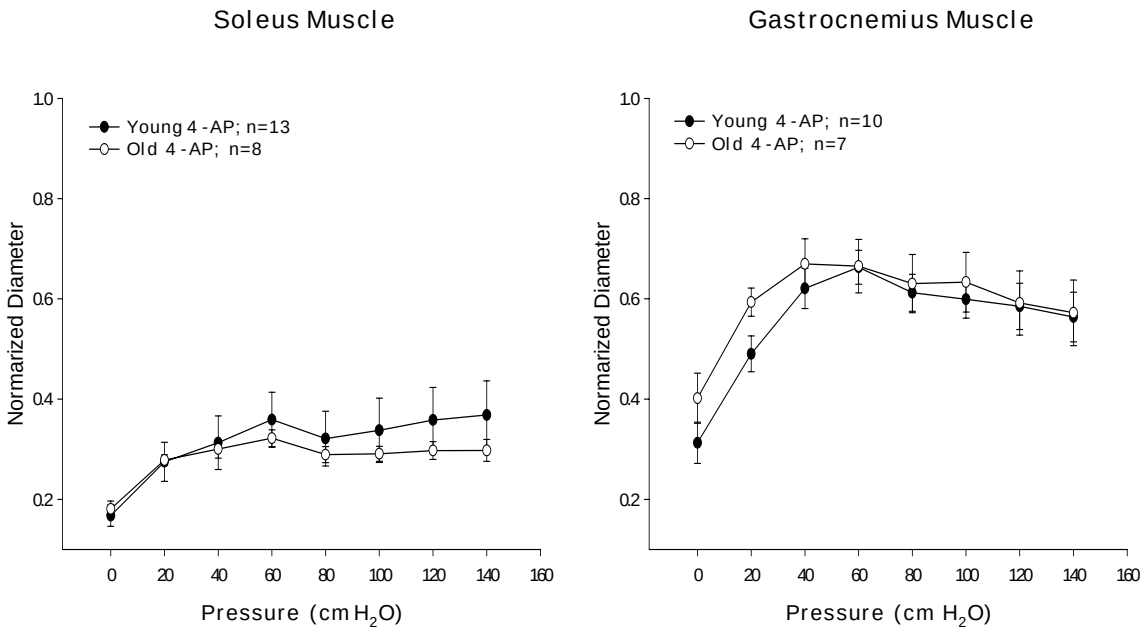

Figure 2. Myogenic response of soleus and gastocnemius muscle arterioles from young and old rats treated with 4-AP (5 mM). In the presence of 4-AP, myogenic responses were not different in arterioles from young and old rats.

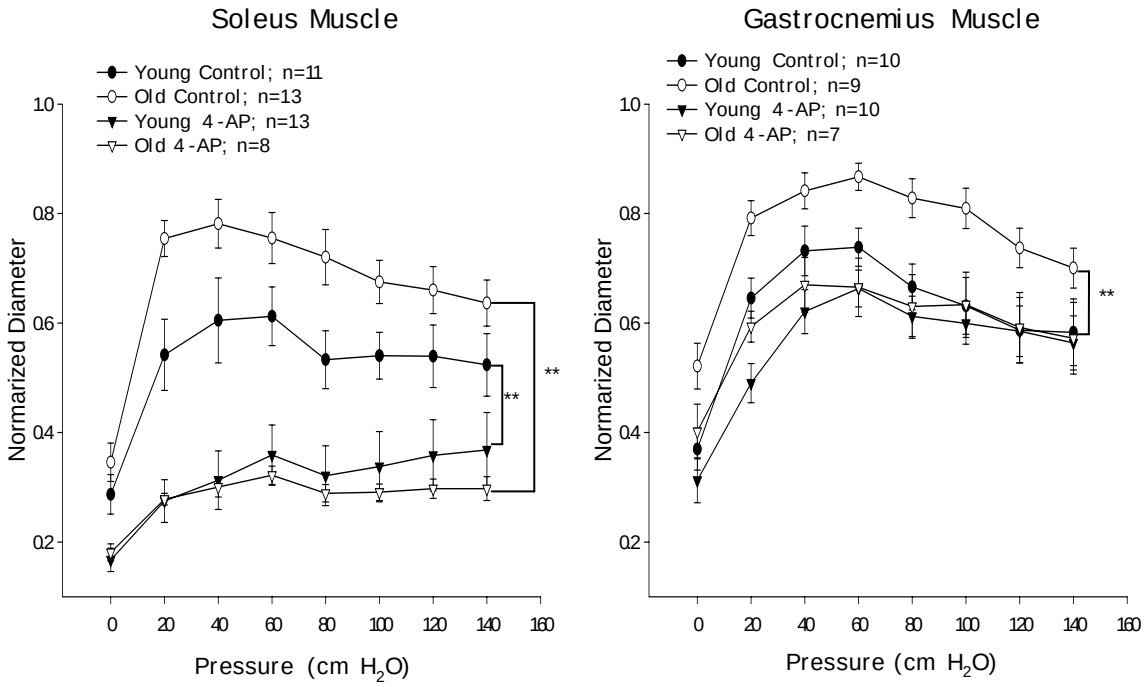

Figure 3. Control and 4-AP treated myogenic responses in skeletal muscle arterioles from young and old rats. Data are presented as means ± SE. **$p < 0.01$, 4-AP vs. control.

Vasoconstrictor Response to K_v Channels Blockade

Figure 4 shows no age related differences in the sensitivity of arterioles from soleus ($p = 0.1993$) and gastrocnemius muscle ($p = 0.7056$) to 4-AP. However, the maximal constriction to 4-AP was greater in soleus muscle arterioles from aged rats.

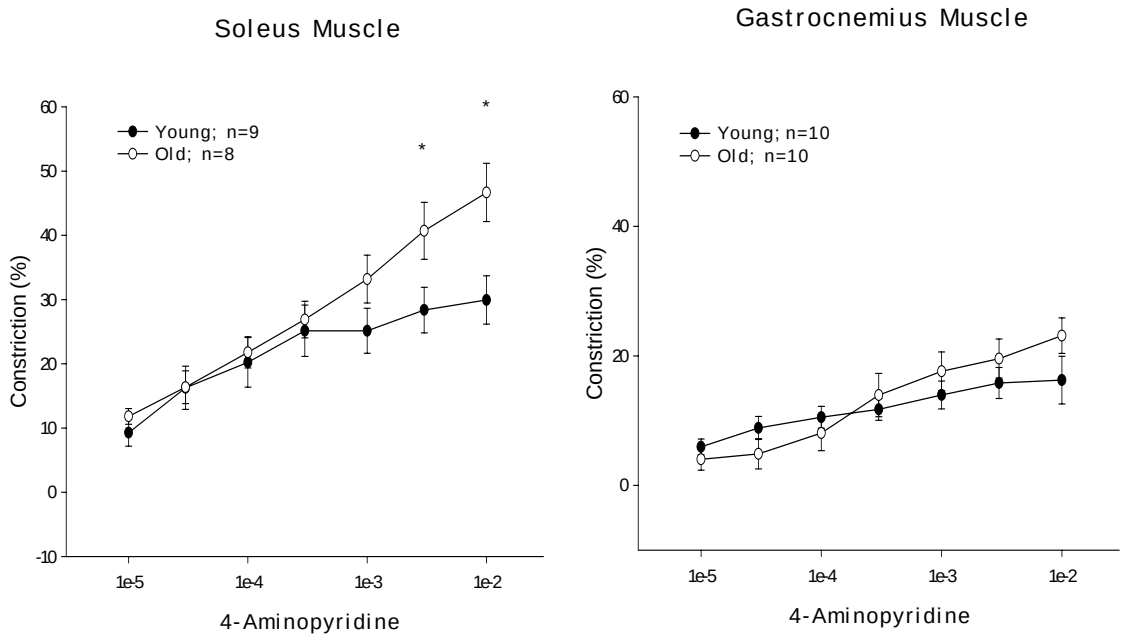

Figure 4. Concentration-response relationship to 4-AP in soleus and gastrocnemius muscle arterioles from young and old rats. In soleus muscle arterioles, maximal constriction to 4-AP was significantly increased by age. Data are presented as means ± SE. *$p < 0.05$, young vs.old.

Contribution of K_{Ca} Channels to Myogenic Response

Figure 5 shows the myogenic response of skeletal muscle arterioles in the presence of K_{Ca} channel blockade with CTX. Age-related differences in the myogenic response persisted in arterioles treated with CTX (Figure 5). CTX significantly increased myogenic reactivity in gastrocnemius muscle arterioles from young and old rats, and CTX significantly increased myogenic constriction of soleus muscle arterioles from young but not old rats (Figure 6).

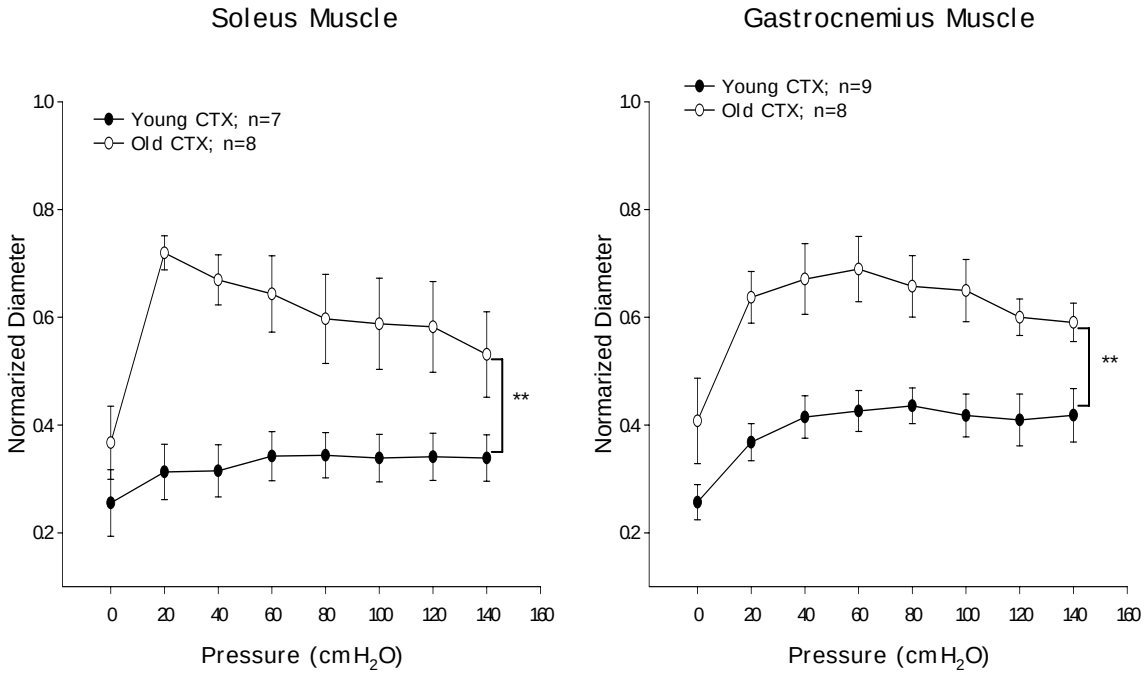

Figure 5. Age-related differences in the myogenic response of soleus and gastocnemius muscle arterioles persisted following treatment with CTX (50 nM). Data are presented as means ± SE. **p <0.01, young vs. old.

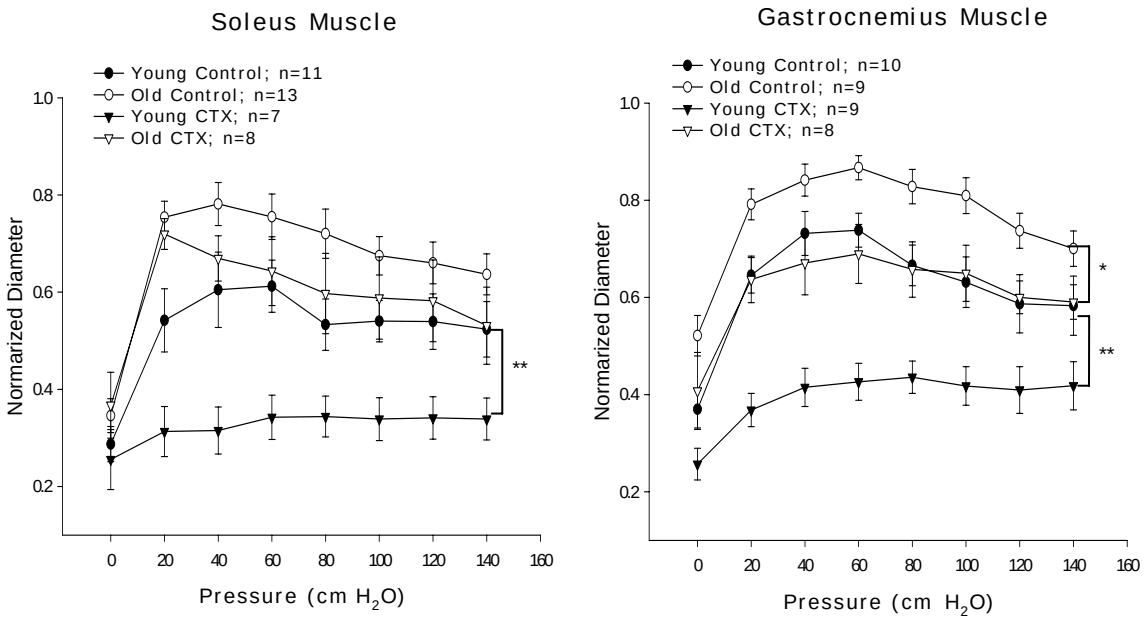

Figure 6. Control and CTX treated myogenic responses of skeletal muscle arterioles. Data are presented as means ± SE. **$p < 0.01$, CTX vs. control, *$p < 0.05$, CTX vs. control.

Vasoconstrictor Response to K_{Ca} Channels Blockade

Figure 7 shows that no age-related differences existed in the constrictor responses to CTX in arterioles from either soleus (p = 0.6197) or gastrocnemius (p = 0.4621) muscle.

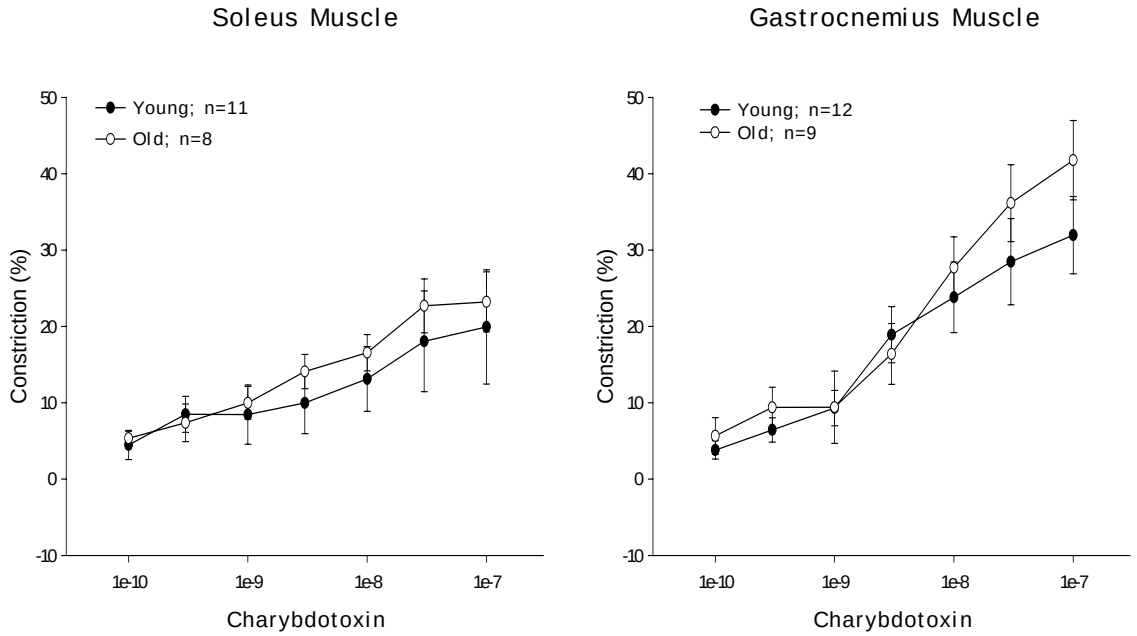

Figure 7. Concentration-response relationship to CTX in soleus and gastrocnemius muscle arterioles from young and old rats.

K^+ Channel Contribution to Myogenic Responsiveness: Effect of Fiber Type

A comparison between constrictor responses of soleus and gastrocnemius muscle arterioles to increasing concentrations of 4-AP is illustrated in Figure 8. 4-AP produced greater constriction of soleus muscle arterioles as compared to gastrocnemius muscle arterioles in both young and old rats.

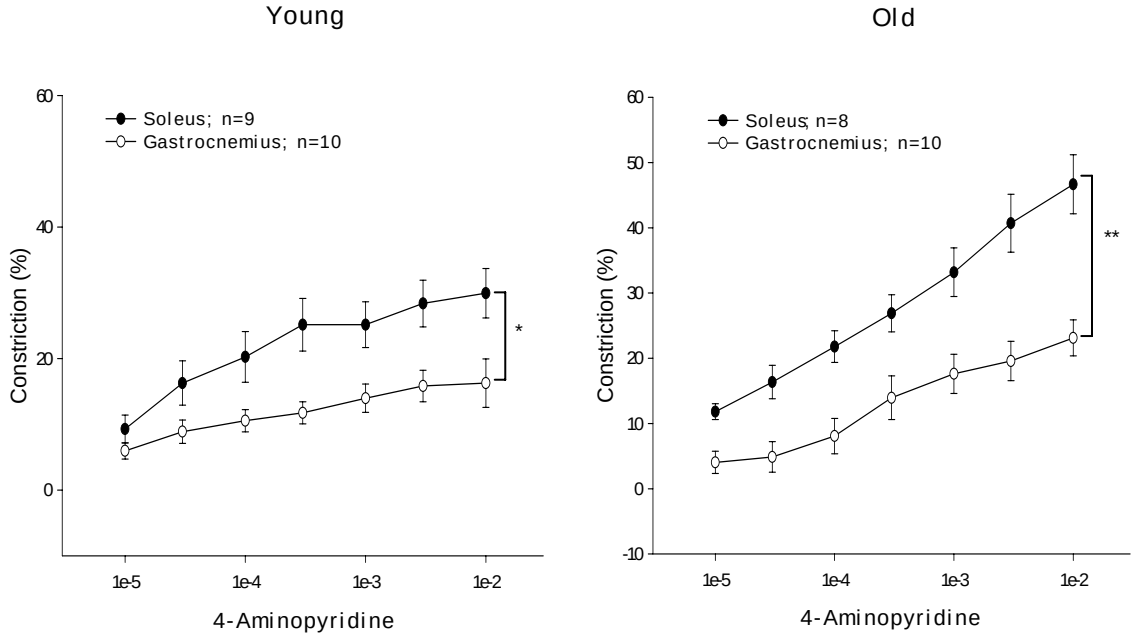

Figure 8. Comparison of constrictor responses to 4-AP in soleus and gastrocnemius muscle arterioles. Constriction to 4-AP was significantly greater in soleus muscle arterioles as compared to gastrocnemius muscle arterioles in both young and old rats. Data are presented as means ± SE. *$p < 0.05$, soleus vs. gastrocnemius muscle, **$p < 0.01$, soleus vs. gastrocnemius muscle.

Comparison of responses to CTX indicated that maximal constriction of gastrocnemius muscles arterioles was greater than that of soleus muscle arterioles in old rats (Figure 9). In young rats, sensitivity to CTX was greater in gastrocnemius muscle arterioles as compared to that of soleus muscle arterioles.

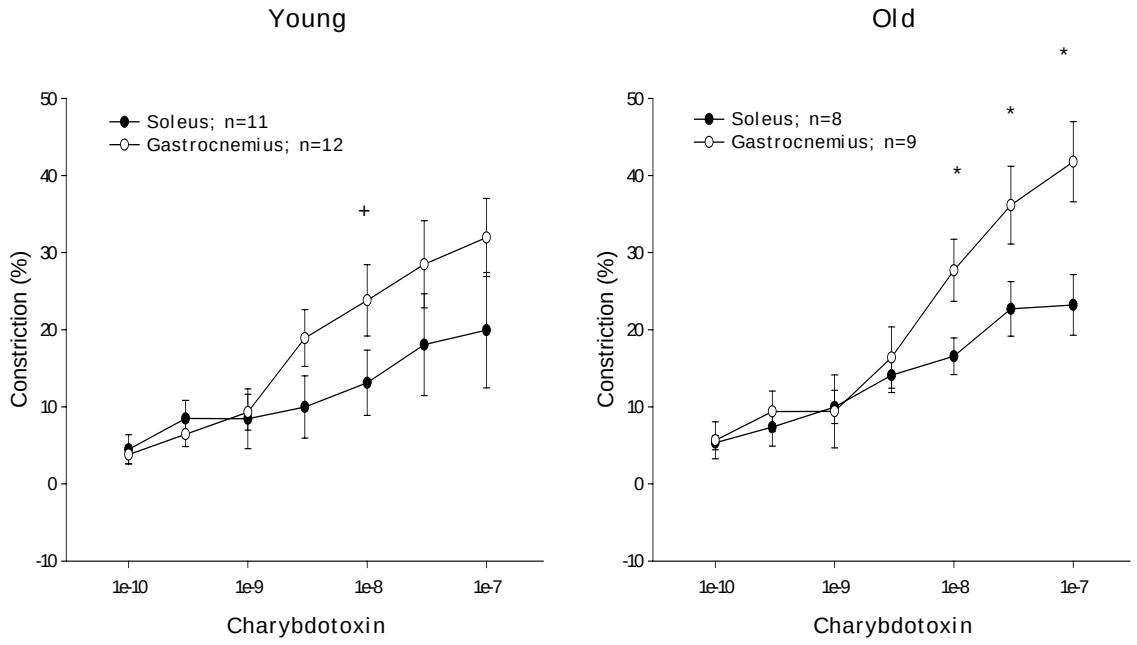

Figure 9. Concentration-response relationships to CTX in soleus and gastrocnemius muscle arterioles from young and old rats. In old rats, maximal constriction to CTX was greater in gastrocnemius muscle arterioles as compared to soleus muscle arterioles. In young rats, sensitivity to CTX was greater in gastrocnemius muscle arterioles as compared to soleus muscle arterioles. Data are presented as means ± SE. *$p < 0.05$, soleus vs. gastrocnemius muscle. +$p < 0.1$, soleus vs. gastrocnemius muscle.

DISCUSSION

The purpose of this study was to determine the role of calcium-activated potassium (K_{Ca}) channels and voltage-gated potassium (K_v) channels in regulation of myogenic tone in intact arterioles from the soleus and gastrocnemius muscles of young (4 mos), old (24 mos) Fischer 344 rats. We hypothesized that increased activity of K_{Ca} or K_v channels reduces the myogenic reactivity of skeletal muscle arterioles from aged Fischer 344 rats. Four main findings emerge from this study. First, we have confirmed our earlier observation that the myogenic response is attenuated in skeletal muscle arterioles from aged rats. Second, increased K_v channel activity contributes to the age-associated reduction of the myogenic response in soleus and gastrocnemius muscle arterioles. Third, alteration of K_{Ca} channel activity in skeletal muscle arterioles dose not contribute to the age-related decrease in myogenic responsiveness. Fourth, the contribution of K_v and K_{Ca} channels to myogenic reactivity varies in arterioles from skeletal muscles of different fiber type. The K_v channel contribution to control of vascular tone is greater in soleus muscle arterioles, whereas the contribution of K_{Ca} channels to maintenance of tone is greater in gastrocnemius muscle arterioles. These data indicate that the mechanisms of myogenic constriction are altered by aging in both soleus and gastrocnemius muscle arterioles, and that the mechanisms of myogenic constriction are muscle specific.

The present data confirm our earlier observations that myogenic responsiveness declines with age in skeletal muscle arterioles (50). Myogenic responsiveness has also been reported to decline with age in human skeletal muscle (50). Age-induced reduction of myogenic responsiveness in skeletal muscle arterioles could impact peripheral vascular resistance during orthostatic challenges (17). Because membrane potential is closely

linked to maintenance of vascular smooth muscle tone, we focused on determining whether increased K^+ channel activity contributed to the age-related decline in myogenic responsiveness of skeletal muscle arterioles.

Various mechanisms have been proposed for transfer of the contractile signal in vascular smooth muscle that occurs in response to distension of the blood vessel wall (49). These include direct activation of ion channels on vascular smooth muscle membrane, modification of biochemical cascade events within vascular smooth muscle cells, length-dependent changes in contractile proteins, and endothelium-dependent regulation of vascular smooth muscle tone (49). Furthermore, numerous studies have shown that myogenic tone is modulated by K^+ channel activity. Selective K^+ channel blockers have been used to determine the negative feedback contribution of potassium channels to control of vascular tone (11). In this study, we found that 4-AP enhanced the myogenic response in both soleus and gastrocnemius muscle arterioles from aged rats to a greater degree than in arterioles from young rats. Furthermore, 4-AP-induced constriction increased with age, whereas CTX-induced constriction was not altered by age. These data suggest that the effects of 4-AP in arterioles from old rats are specifically related to its effects on K_v channels and not to non-specific alteration of membrane potential. These data also suggest that K_v channels play an increasingly important role in control of vascular smooth muscle tone with age.

Aminopyridines do not indirectly modulate the release of factors from the endothelium or prevascular nerves that could alter smooth muscle membrane potential and arterial diameter (41). For instance, removal of the endothelium and addition of a variety of receptor blockers had little effect on pressure-induced constrictions or the

constrictions caused by 4-AP (41). Thus, 4-AP-induced constrictions are not mediated by agonists, i. e., norepinephrine, accetylcholine, serotonic, and histamine, or endothelial factors (41). Furthermore, membrane potential depolarization to 4-AP was unaffected by the calcium channel inhibititors, diltiazem or nisoldipine, at concentrations that would cause maximal dilation (12) and substantial inhibition of calcium channels (65), and K_{Ca} channels (57). These findings suggest that these aminopyridines act independently of altering the activity of K_{Ca} channels and calcium channels (41). Therefore, the role of K_v channels in modulation of myogenic activity is directly linked to membrane potential, and the K_v channel blocker, 4-AP, acts as a specific inhibitor of K_v channels and membrane hyperpolarization. Our data indicate that 4-AP eliminated age-associated differences in myogenic constriction. To further determine whether sensitivity or maximal responses to K^+ channel blockade changed with age, vasoconstrictor responses to pharmacological blockade of K_v channels were determined. Our results also show that the maximal constrictor responses to the K_v channel blocker, 4-AP, were greater in skeletal muscle arterioles from old rats. Thus, we provide evidence that the age-related reduction of myogenic constriction in skeletal muscle arterioles is due to, at least in part, to increased K_v channel activity that occurs in response to increases in transmural pressure.

In coronary arterioles from exercise trained pigs, Bowles et. al., (9) found that enhanced myogenic constrictor responses were accompanied by an increased K^+ channel contribution to basal tone. Exercise training also increased VGCC activation, and BAY K 8644, an activator of VGCC, potentiated TEA-induced contractions (9). These authors postulated that exercise training enhances membrane depolarization and VGCC

activation, with a concomitant increase in K_v and K_{Ca} channel activation and increased negative feedback, limiting vascular smooth muscle depolarization and constriction despite an overall increase in basal tone. In contrast, we have found that age increases the K_v channel activation during myogenic constriction, contributing to a net decrease in myogenic tone.

Contrary to our hypothesis, Figure 6 shows that the K_{Ca} channel contribution to the myogenic response decreased in arterioles from aged rats. CTX was more effective in enhancing myogenic tone response in skeletal muscle arterioles of young rats. When transmular pressure increases, in addition to Ca^{2+} entry directly through stretch-activated channels, membrane depolarization activates VGCC, allowing Ca^{2+} influx and vascular smooth muscle contraction (9). Ca^{2+} influx activates K_{Ca} channels, which act as a brake on vasoconstriction through limitation of depolarization, VGCC activation and contraction (11). We hypothesized that an age-related increase of K_{Ca} activation would reduce myogenic constriction of skeletal muscle arterioles. Instead, we found evidence of reduced K_{Ca} activation during exposure to increasing transmular pressure. Our data indicate that K_{Ca} channel activation does modulate myogenic constriction in skeletal muscle arterioles, but enhanced activation of these channels does not occur with age. In contrast in coronary arteries the occurance of spontaneous contraction (vasospasm) is more frequent in aged subjects (46). Subjects at risk for coronary vasospasm show decreased K_{Ca} channel expression as age progresses; protein levels of these channels in coronary smooth muscle decreased with age in both rats and humans (46). It has also been reported that function, protein levels, and pharmacological characteristics of K_{Ca} channels diminish in coronary myocytes of old rats (54). Although an increase in K_{Ca}

channel activity dose not appear to contribute to the age-related reduction in myogenic responsiveness, our data do indicate that age alters K_{Ca} channel activity in skeletal muscle arterioles. Our finding that CTX enhancement of myogenic constriction declines with age is consistent with reports of an age-related decrease in K_{Ca} channel activity in coronary myocytes and smooth muscle (54).

The results of this study also indicate that the intrinsic ability of blood vessels to respond to changes in transmular pressure is differentially regulated in resistance arterioles from muscles composed of different fiber types, e. g., the highly oxidative soleus muscle and the glycolytic superficial portion of the gastrocnemius muscle. Mammalian muscles are comprised of different fiber with varying characteristics (55). Different types possess specific myosin heavy-chain composition and biochemical and physiological properties (3). Therefore, investigation of muscles of distinct fiber type with differential vascular responses is necessary in order to establish the effects of fiber composition on muscle function (19). Blood flow patterns at rest and during exercise differ between these muscles (19), and several studies have shown that vascular responses to both dilators and constrictors differ between resistant arterioles in soleus and gastrocnemius muscle (47, 50, 51). Endothelium-dependent vasodilation to acetylcholine decreases with age in soleus muscle arterioles but not in gastrocnemius arterioles (51, 59, 64). Myogenic reactivity is reduced in gastrocnemius muscle arterioles but not in soleus muscle arterioles of hindlimb unloaded rats, suggesting exposure to microgravity produces muscle-specific alterations of vascular smooth muscle (18). Our findings indicate that age produces similar mechanistic changes in vascular smooth muscle of soleus and gastrocnemius muscle arterioles; however, the K^+ channel contributions to

myogenic constriction differ in arterioles from these two muscles. Further work will be necessary to determine the whether age alters K^+ channel expression in vascular smooth muscle of skeletal muscle arterioles, and the signaling mechanisms that stimulate changes in K^+ channel activity with age.

In conclusion, this study indicates that K_v and K_{Ca} channels are tonically active in skeletal muscle arterioles contributing to a hyperpolarizing force that opposes myogenic constriction. Our data indicate that increased K_v channel activity contributes to reduced myogenic constriction in soleus and gastrocneius muscle arterioles from aged rats. K_{Ca} channel activity opposes myogenic tone in young but not old rats in soleus muscle arterioles, and in gastrocnemius muscle arterioles, the K_{Ca} channels contribution to myogenic tone is greater in arterioles from young as compared to old rats. Thus, age-related changes in pressure-induced K_v channel activity is not likely to be linked to altered membrane potential or Ca^+ mechanisms that regulate Ca^{2+} influx, because K_{Ca} channel activity was not increased with age. In addition, the contribution of K_v and K_{Ca} channels to the myogenic response differs in arterioles from the highly oxidative soleus muscle and the highly glycolytic gastrocnemius muscle. This finding support previous evidence that the vascular response to various stimuli varies between skeletal muscles of differing fiber type. Therefore, both age and fiber type influence myogenic reactivity in skeletal muscle arterioles.

SUMMARY AND CONCLUSIONS

The purpose of this study was to determine the role of calcium activated potassium channels (K_{Ca}) and voltage-gated potassium channels (K_v) in regulation of myogenic tone in intact arterioles from the soleus and gastrocnemius muscles of young (4 mos), old (24 mos) Fisher 344 rats. Our work indicates that 1) K_v and K_{Ca} channels are tonically active in skeletal muscle arterioles, contributing to a hyperpolarizing force that opposes myogenic constriction, 2) increased K_v channel activity contributes to reduced myogenic constriction in soleus and gastrocnemius muscle arterioles from aged rats, 3) in soleus muscle arterioles, K_{Ca} channel activity opposes myogenic tone in young but not old rats, 4) in gastrocnemius muscle arterioles, the K_{Ca} channel contribution to myogenic tone is greater in young compared to old rats, and 5) myogenic constriction is differentially regulated in resistance arterioles from muscles composed of different fiber types, e. g., the highly oxidative soleus muscle and the glycolytic superficial portion of the gastrocnemius muscle. Therefore our findings indicate that the modulation of myogenic tone by K^+ channels differs between soleus and gastrocnemius muscle arterioles; however, in arterioles from both soleus and gastrocnemius muscle the contribution of K_v channels to regulation of myogenic tone increases with age.

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