Sex-specific differences in cerebral arterial myogenic tone in hypertensive and normotensive rats

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BLOOD FLOW (BF) autoregulation, the inherent ability of vascular beds to maintain constant flow despite changes in arterial pressure, is a feature of the cerebral circulation (34). Cerebral blood flow (CBF) is regulated by multiple control mechanisms encompassing metabolic factors, neural influences, flow-mediated dilation, and pressure-induced myogenic constriction. Myogenic tone is generated by smooth muscle (SM) of small arteries and arterioles that contracts to increased pressure and relaxes in response to decreased pressure. Although initially described in vivo, myogenic constriction is also observed in isolated blood vessels, illustrating that mechanisms inherent to the vascular wall are sufficient to induce the myogenic response. Thus myogenic reactivity is an important determinant of vascular tone and BF.

Stroke is a complex event encompassing cerebral infarction and intracerebral hemorrhage with important contributory roles for chronic vascular disease and cerebral ischemia (12). Abundant evidence supports a strong association between stroke and hypertension (11), and, specifically, elevated BP can increase the likelihood of stroke by compromising cerebral function. CBF autoregulation is an important protective mechanism against edema of the brain and hemorrhagic stroke when systemic pressure rises or against hypoxia and ischemic stroke when systemic pressure falls. At present, it is not clear whether myogenic tone abnormalities are a cause or consequence of elevated pressure or indeed independent of pressure (39), but dysregulated myogenic activity can disrupt local hemodynamic patterns in the cerebral microvasculature and thus facilitate stroke events (33, 37, 38).

Sex-dependent differences are emerging as an important regulatory influence in the incidence and development of cardiovascular diseases, including stroke, hypertension, and atherosclerosis (27). Although myogenic autoregulation is considered to rely on the intrinsic ability of arterial SM to respond to changes in perfusion pressure, endothelial-derived modifiers have also been proposed to be important. Negative roles for nitric oxide (NO) and estrogen in myogenic tone development have been identified in female rats (17), but myogenic tone has also been shown not to differ between sexes (36). Sex-specific effects on cerebral myogenic responsiveness in hypertension, however, have not been previously reported.

Spontaneously hypertensive rats (SHR) that are stroke prone (SHRSP) are genetically predisposed to cerebral ischemia and hypertension and exhibit increased sensitivity to experimentally induced stroke compared with WKY, the normotensive strain from which SHRSP are derived (43). Furthermore, myogenic tone of resistance arteries is likely to be subjected to differing modulatory influences in hypertensive and normotensive animals. Characterizing cerebral myogenic properties in the clinically relevant SHRSP (43) model is therefore important to further understand stroke pathogenesis and recovery processes initiated after stroke events, an increasingly important aspect of stroke research (28). Here, we examined the hypothesis that myogenic cerebral vascular control is impaired in SHRSP relative to WKY rats in a sex- and strain-specific manner.

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METHODS

Twelve-week-old SHRSP and WKY rats maintained on standard rat chow were obtained from in-house colonies, established by brother-and-sister mating (10). BP was measured by tail-cuff plethysmography 1 wk before experimentation, as described (10). Experiments were approved by the Home Office in accordance with animal experimentation guidelines of the United Kingdom.

Middle Cerebral Arteries Preparation

On the day of the experiment, rats were weighed and anesthetized by intraperitoneal injection of pentobarbital sodium (50 mg/kg). Brains were removed and placed in physiological saline solution (PSS) containing (in mM) 118.4 NaCl, 4.7 KCl, 2.5 CaCl₂, 1.2 KH₂PO₄, 1.2 MgSO₄, 25 NaHCO₃, and 11.1 glucose, gassed with 95% O₂-5% CO₂ at 4°C. Middle cerebral arteries (MCA) were dissected and prepared for pressure-myography (Living Systems), as described (19). Preliminary tests were performed to assess vascular contractility (10⁻⁵ M norepinephrine) and endothelium-dependent relaxation (3 x 10⁻⁶ M acetylcholine choline) to ensure endothelial integrity. Vessels were equilibrated in PSS at 37°C for 60 min at specific [50% of systolic BP (SBP)] of intraintraluminal pressures (IPs). Vessels were set to 50% systolic pressure to approximate in vivo pressures (2) and to optimize development of constrictor tone. Leaky vessels, identified by a fall in vessel pressure when the pressure servo-control, which controls IP, was switched to manual mode to remove automatic control of pressure, were excluded from the study.

Experimental Protocol

IP was reduced to 20 mmHg and then increased in 20 mmHg increments to 200 mmHg in a stepwise manner. Vessels were allowed to stabilize at each pressure for 5–10 min. Measurements of vascular wall thickness did not include the adventitial layer and are approximately the media thickness (MT; endothelial thickness of ~2 μm is included). MT and internal lumen diameters (ID) were measured at four equidistant points along the vessel segment with a video-dimension analyzer, and the results were averaged. PSS was then replaced with calcium-free/EGTA PSS (same composition as PSS with CaCl₂ omitted and with 1 mM EGTA added), and pressure curves were repeated in calcium-free PSS to determine passive vascular characteristics.

Data Analysis

Percent myogenic responses at each pressure were determined from IDₚ/ID₀ × 100, where IDₚ is the ID measured in PSS and ID₀ is the ID measured in calcium-free PSS. Slopes of the myogenic-pressure curves for individual vessels were determined by linear regression.

Vascular mechanical characteristics (18) and remodeling indexes (2, 21) were determined in passive calcium-free conditions, as previously described. Circumferential stress (σ) was calculated from (IP × ID)/2MT, where ID is a given IP. Pressure was converted (from mmHg to dyn/cm²) as follows: 1 mmHg = 1.334 x 10⁵ dyn/cm². Circumferential strain (ε) was calculated from (ID - ID₀)/ID₀, where ID₀ is original ID (measured at 10 mmHg IP). Elastic modulus reflects the intrinsic elastic properties of the wall material (independent of vessel geometry) and was determined from stress-strain data for individual vessels fitted to exponential curves (y = a₀eᵇₓ), using least-squares analysis. σ = σ₀eᵇₓ, where σ₀ is the stress at the ID₀, and β is the slope of the stress-strain curves (a higher β value is indicative of a stiffer vessel). Tangential elastic modulus (ET) was calculated at several values of stress from the derivative of the exponential curve: ET = dσ₀/dε = βσ₀eᵇₓ.

Percent media-to-lumen ratios were calculated from MT/lumen diameter × 100.

Remodeling index was defined as the percentage of the observed differences in the ID of hypertensive (ID₀) and normotensive (ID₀) vessels that can be accounted for by remodeling of the normotensive vessels and calculated as described (2, 21). Remodeling index = 100 (ID₀ - IDremodel)/(ID₀ - ID₀), where IDremodel is the remodeled ID. IDremodel = sqrt (EDh² - 4CSAh/π), where EDh is the external diameter of hypertensive vessels and CSAh is the cross-sectional area of normotensive vessels.

Growth index (21) was calculated as (CSAh - CSA₀)/CSAh, where CSA₀ is the CSA of hypertensive vessels. Media CSA was obtained by the subtraction of internal CSA from external CSA, i.e., CSA = π (ED² - ID²)/4.

Statistical Analysis

Values are means ± SE. One vessel per rat was used for analyses. Differences between vessels were assessed by repeated-measures ANOVA (RMANOVA) or two-way (strain and sex) ANOVA with Fischer test for post hoc comparisons. Unpaired t-tests were used for comparisons between two groups. P < 0.05 was considered statistically significant. Statistical analysis was performed with the StatView 5.0 package (Abacus Concepts, Berkeley, CA).

RESULTS

BP and Body Weight

Baseline SBP and body weights are shown in Table 1. No sex-dependent differences in SBP were detected in WKY rats, but in contrast male SHRSP exhibited significantly higher SBP than females. SBP was also significantly higher in SHRSP males and females compared with their WKY counterparts. Body weight in both strains was significantly greater in males than in females. A comparison of strains in males showed that SHRSP were significantly lighter than WKY rats, but there were no strain-dependent differences in female body weights.

Pressure-Diameter Relationships

Effects of sex-dependent differences. In active conditions, WKY vessel pressure-diameter relationships were significantly different (P < 0.05) between sexes at pressures >120 mmHg, because myogenic tone was more prominent in females compared with males (see Myogenic Tone as a Function of Intra-vascular Pressure). In SHRSP vessels, pressure-induced re-

Table 1. Baseline SBP and body weights of WKY and SHRSP

<table>
<thead>
<tr>
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<th>Males</th>
<th>Females</th>
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<tr>
<td></td>
<td>WKY</td>
<td>SHRSP</td>
</tr>
<tr>
<td>SBP, mmHg</td>
<td>123.83 ± 2.55</td>
<td>169.33 ± 3.85</td>
</tr>
<tr>
<td>Body weight, g</td>
<td>289.83 ± 19.45</td>
<td>235.67 ± 5.81</td>
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Values are means ± SE. SBP, systolic blood pressure. *P < 0.05, †P < 0.005, and ‡P < 0.001 for stroke-prone spontaneously hypertensive rats (SHRSP) vs. corresponding Wistar-Kyoto rats (WKY); †P < 0.05 and ‡P < 0.005 for males vs. females.
ductions in diameter were enhanced in females compared with males, although the pressure-diameter relationships did not differ because male vessels were smaller (see Myogenic Tone as a Function of Intravascular Pressure).

In passive conditions, WKY vessel diameters in males tended to be greater than in females, although the pressure-diameter relationships were not significantly different (Fig. 1A). Pressure-diameter relationships in SHRSP also tended to differ between sexes at pressures >100 mmHg (female vessel diameters were greater), but again the differences were not significant (Fig. 1B).

Strain-dependent differences. In active conditions, pressure-diameter relationships in males and females differed significantly between WKY and SHRSP (see Myogenic Tone as a Function of Intravascular Pressure). In passive conditions, there were also major strain-dependent differences in pressure-diameter relationships between sexes, attributed to smaller SHRSP vessel diameters (Fig. 1, C and D).

Myogenic Tone as a Function of Intravascular Pressure

Myogenic tone as a function of pressure revealed the extent of constrictor tone, shown by vessel diameter reductions in active relative to passive conditions (Fig. 2). RMANOVA in the pressure range 120–160 mmHg showed significant differences between sexes (P < 0.01) and strain (P < 0.05) on myogenic tone.

Further analyses of slopes of the myogenic tone-pressure curves in selected pressure ranges (shown in Fig. 2) demonstrated significant sex-dependent differences. In both strains, slopes in males were greater than those in females, indicating a negative influence of male sex on myogenic tone development (Fig. 2, A and B).

There were no strain-dependent differences in males, but in females slopes in WKY rats were significantly (P < 0.05) greater than in SHRSP (note negative slopes in SHRSP) (Fig. 2, C and D).

Myogenic Index

Myogenic index, determined from slopes of the myogenic-pressure curves for individual vessels in the pressure intervals exhibiting no gain or loss in diameter, is inversely related to myogenic strength. Myogenic indexes exhibited significant sex-dependent differences but did not differ between strains. In both WKY and SHRSP strains, males exhibited significantly greater myogenic indexes than females (Fig. 3A). Notably, myogenic indexes in females of both strains were negative, whereas they were positive in males, indicating that the myogenic response is comparatively weaker in males.

Sex difference and strain were both important determinants in the yielding of myogenic tone, (loss of pressure-mediated constriction). Male vessels in both WKY and SHRSP yielded at significantly lower pressures than in female vessels. In WKY vessels, yielding of tone occurred at 140 and 180 mmHg in males and females, respectively. In SHRSP vessels, yielding occurred at comparatively lower pressures, i.e., 120 and 140 mmHg in males and females, respectively.

![Pressure-diameter relationships for middle cerebral arteries in passive (calcium free) conditions. A and B: no sex-dependent differences in stroke-prone spontaneously hypertensive rat (SHRSP; P > 0.1) or Wistar-Kyoto rat (WKY; P > 0.1) vessels. C and D: significant strain-dependent differences between vessels in males (P < 0.005) and females (P < 0.01). Number of vessels is given in parentheses.](http://ajpheart.physiology.org/.)
A plot of myogenic index as a function of SBP (Fig. 3B) demonstrated no evidence of a relationship between these parameters. Hence, SBP does not appear to be a significant determinant of myogenic index, although it may be a contributory factor in a different phase of development.

Mechanical Properties

MCA stress-strain relationships were determined in passive (calcium free) conditions to evaluate wall distensibility properties. Vascular wall distensibility was in the following order: female SHRSP > male WKY > male SHRSP ~ female WKY.

Sex-dependent differences. In WKY rats, vessels were more distensible in males than in females, as demonstrated by leftward shift of female stress-strain curves (Fig. 4A). The converse was observed in SHRSP (Fig. 4B). ETs (β, the rate constant of stress-strain curves) were determined for several stresses from the stress-strain relations, as a further illustration of vessel stiffness (Fig. 4, C and D). For WKY vessels, β values were $4.1 \pm 1.0$ and $6.6 \pm 1.2$ ($P = 0.05$) in males and females, respectively; and for SHRSP vessels, β values were $5.1 \pm 0.8$ and $3.2 \pm 0.7$ ($P < 0.05$) in males and females, respectively. Thus the decreased ETs in male WKY compared with those in females reflect the decreased stiffness of male arterial walls. In SHRSP, the sex differences in vascular stiffness were opposite to those in WKY rats.

Strain-dependent differences. Comparison of strains in males indicated that SHRSP vessels were less distensible than WKY vessels (Fig. 4, A and B). Conversely, in females, WKY vessels were stiffer than SHRSP vessels. ETs did not differ between strains in males, but in females, in contrast, exhibited significant strain-dependent differences (Fig. 4, C and D). Thus, in males, β values were $4.1 \pm 1.0$ and $5.1 \pm 0.8$ ($P = 0.49$) in WKY and SHRSP vessels, respectively; in females, β values were $6.6 \pm 1.2$ and $3.2 \pm 0.7$ ($P < 0.05$) in WKY and SHRSP vessels, respectively.

It should be noted that unstressed vessel diameters used to calculate stress for stress-strain curves were measured at 10 mmHg, whereas diameters at 0 mmHg are completely unstressed. Further analyses based on diameters at 0 mmHg, derived by extrapolation of individual pressure-diameter
curves, however, showed the same intergroup differences between stress-strain curves.

Wall Tension and Stress

Sex-dependent differences. Wall tension in active conditions as a function of pressure is depicted in Fig. 4, E and F. In both strains, wall tension was similar between sexes. However, at pressures >140 mmHg in WKY vessels, wall tension in males was higher compared with females (P < 0.05), presumably due to the attenuated myogenic constrictor tone in males.

Passive wall stress as a function of pressure revealed no differences between sexes in WKY rats (Fig. 4, G). In SHRSP vessels at distending pressures of 120–180 mmHg, however, males exhibited lower wall stress than females, although this difference was not apparent in active conditions due to the greater myogenic tone in females (Fig. 4H).

Strain-dependent differences. Wall tension in SHRSP vessels was significantly lower in males (P < 0.001) and females (P < 0.01) compared with their WKY counterparts, indicating adaptation of SHRSP vessels to elevated BP (see Vascular Structural Properties and Fig. 4, E and F). Passive wall stress in SHRSP was also significantly lower than in WKY male (P < 0.001) and female (P < 0.001) counterparts (Fig. 4, G and H).
Vascular Structural Properties

Vascular structural comparisons were made in passive conditions at 100 mmHg (approximate in vivo mean pressure of MCA in male SHRSP) distending pressure. Lumen diameters did not differ between sexes in either strain (Fig. 5A). A comparison of strains showed that vascular lumens were markedly smaller than their WKY male [95% confidence interval (CI) 163–227 and 246–308 μm, respectively] and female (95% CI 190–224 and 239–289 μm, respectively) counterparts.

Media-to-lumen ratios of MCA were in the following order: male SHRSP > female SHRSP > male WKY > female WKY. In males of both strains, media-to-lumen ratios tended to be moderately higher compared with those of females (Fig. 5B). A comparison of strains in males showed that media-to-lumen ratios were higher in SHRSP than in WKY rats (95% CI 11.36–17.95 and 7.76–11.38, respectively). Similarly, media-to-lumen ratios in females were higher in SHRSP than in WKY rats (95% CI 11.57–14.56 and 6.87–9.08, respectively). Similarly, media-thickness in SHRSP was significantly greater than in WKY vessels. There were no differences between sexes.

In males of both strains, vascular lumen diameters at low distending pressures in passive conditions tended to converge (Fig. 1C), indicating that structural differences at physiological pressures are primarily attributable to differential wall distensibility. Remodeling indexes of MCA of male SHRSP were 107%, reflecting the reduced distensibility of MCA in SHRSP. In females, vascular lumen diameters at low pressures remained distinct between the strains (Fig. 1D), confirming the structural basis of vascular differences at physiological pressures. Remodeling indexes of 84%, together with growth indexes of 9%, were exhibited by female SHRSP.

DISCUSSION

The major findings of this study are that sex and strain are important determinants of cerebral vascular myogenic tone and mechanical properties. Specifically, myogenic reactivity is reduced in males compared with female counterparts in both strains, and strains do not differ in males, whereas in females myogenic tone is enhanced in SHRSP compared with WKY rats. Vascular stiffness is reduced in males compared with females in WKY rats, but the converse is observed in SHRSP, and the comparison of strains in males showed that vascular stiffness is accentuated in SHRSP, whereas in females, stiffness is profoundly reduced in SHRSP compared with WKY counterparts.

Sex-specific influences on vascular myogenic properties in normotensive rodents have mostly shown attenuated myogenic responses in females, attributed to factors such as increased estrogen (17), reduced superoxide production (9), or possibly altered SM calcium handling (30). Sex-dependent differences in myogenic tone in SHR/SHRSP or WKY rats, however, have not been previously reported. Our findings demonstrate that WKY female vessels are markedly stiffer, and myogenic responsiveness is enhanced compared with males. Extended limits of myogenic regulation in WKY females suggest a greater capacity for cerebral flow autoregulation than in males and more effective buffering of capillary pressure from elevations in systemic pressure. Because NO is produced more efficiently in WKY females (13) and is expected to attenuate myogenic tone (42), additional mechanisms are likely involved in the vessels studied here. In SHRSP, female vessels elicit...
significantly greater myogenic tone and are more distensible compared with those in male counterparts. Furthermore, the myogenic interval in females extends over a greater pressure range, and yielding pressure is comparatively elevated. Thus female SHRSP vessels exhibit an improved capacity to adapt to elevated pressure and to regulate BF by myogenic mechanisms.

The menstrual cycle and altering systemic levels of reproductive hormones also need to be considered in females. There is abundant evidence for cyclical changes in gonadal hormones and NO synthase (NOS) induction in several tissues (41). In rats (estrus cycles of ~4 days), NOS levels in reproductive tissues, which fluctuate over the cycle (4), are directly influenced by estrogen levels (5, 17, 36), and, moreover, NOS activity (4, 5, 29, 31) varies with estrus progression. Intriguingly, all the NOS isoforms are regulated by the estrus cycle (5). Of particular relevance to the vasculature, distinct changes in vasoactive hormones, such as NO (29, 31), prostanoids (44), vasopressin (7), and vascular function (8), occur as estrus progresses. We did not determine the stage of estrus in females, and random cycling is a potential source of variation in the data. Examination of myogenic tone and fluctuations in vascular protein and gene expression, in association with the estrus cycle, would advance understanding of cerebrovascular dysfunction and possibly stroke pathogenesis.

Cerebral myogenic tone characteristics of SHR (22, 32), but not SHRSP, have been compared with those of WKY rats. We found that myogenic vasoconstriction in male SHRSP before yielding pressure is similar to that in WKY counterparts, despite exposure to higher BP. Male SHRSP vessels are also stiffer and yield myogenic tone at lower pressure than do WKY vessels. Large posterior cerebral arteries (CA) in males are also stiffer in SHRSP than in WKY, but the converse is observed in small CAs (~100 μm), indicating that they are differentially regulated (18). Cerebral myogenic tone in male SHR, which are stroke-resistant, yields at a pressure higher than that in SHRSP (23), suggesting that lower yielding pressures facilitate stroke-related events. Increased stiffness and inappropriate myogenic adaptation in male SHRSP are potential disrupting factors in BF autoregulation. In periods of abrupt flow reduction or increase, restricted dynamic reactivity in stiff vessels may increase stroke-related ischemic or hemorrhagic events. In particular, the upper limit of pressure at which CBF regulation can proceed in SHRSP is reduced and may cause overperfusion and disruption of the blood-brain barrier.

In females, SHRSP vessels are markedly more distensible than WKY vessels, but yielding of myogenic tone occurs at lower pressure. Before attaining yielding pressure, female SHRSP maintain greater myogenic constriction than their WKY counterparts, which likely protects against elevated BP. Enhanced myogenic reactivity in SHRSP may be attributed to endothelial dysfunction (13), attenuating important negative modifiers (e.g., NO) and/or augmenting constrictor tone enhancers (e.g., superoxide).

Hypertension is associated with increased arterial stiffness, but the evidence is not entirely consistent. Vascular distensibility is determined by internal elastic laminae and elastin content/distribution (3), the network of cellular and extracellular wall components, and gonadal hormones, such as estrogen and androgens, which can influence SM growth and/or matrix composition (14). Although most studies have been undertaken in large conduit vessels, it is likely that estrogen and/or NO-induced (16) inhibition of SM (predominant wall component) growth also affects small arterial distensibility. We found vascular stiffness was not related to SBP, sex, or myogenic responsiveness, suggesting that stiffness is an inherent vascular feature. Conceivably, there is a possible role for adaptation to elevated pressure or wall tension, but the sex dimorphism exhibited within the normotensive and hypertensive strains with similar wall tensions suggests that alternative factors, such as genetics, are overriding influences.

Several studies have proposed that myogenic tone is augmented in hypertension, but the evidence remains equivocal and is further complicated by considerable heterogeneity among vascular beds. Thus cerebral vessels in hypertension exhibit enhanced (20), similar (15), or weakened (32) myogenic responsiveness compared with vessels in normotension. Myogenic constriction and/or vascular stiffness can modify wall tension and thereby protect the vasculature. Either mechanism can restore wall stress, but increased stiffness, as in male SHRSP, is undesirable for BF autoregulation. In the present study, comparable levels of tension in WKY and SHRSP vessels in both sexes suggest a regulatory role for specific mechanosensors. SM can release 20-hydroxyeicosatetraenoic acid in response to tension, which, in turn, induces the release of substance P from sensory nerves, causing SM constriction (35). Intriguingly, cerebral vascular substance P innervation in males is reduced in SHRSP compared with WKY rats (25), though the neuronal pattern in females is presently unclear.

Cerebral vascular structure is an additional factor for consideration in stroke pathogenesis. We found that MCA in male SHRSP exhibit inward eutrophic remodeling associated with reduced distensibility. MCA in female SHRSP exhibit inward hypertrophic remodeling (~85% reduction in ID by eutrophic remodeling and ~10% by hypertrophic remodeling). Wall thickness of MCA in male SHRSP is not increased compared with WKY counterparts, as also reported in MCA (26, 40) and in posterior CA (18) of a comparable size to vessels studied here. Although the absence of wall thickening in SHRSP is a possible predisposing factor for stroke, it is noteworthy that wall stress in SHRSP is comparatively reduced (because ID are smaller).

Our findings have important implications for the enhanced sensitivity to cerebral ischemia in male SHRSP compared with WKY counterparts (6, 24) and for the increased incidence of stroke in SHRSP (28, 43). Infarct size after MCA occlusion was in the following order: male SHRSP > female SHRSP > male WKY > female WKY and, notably, not related to BP. Myogenic abnormalities in males may contribute to larger cerebral infarctions. Previous investigations (1) into sex-specific responses to brain injury from cerebral focal ischemia and stroke have proposed neuroprotective and flow-preserving effects of endogenous estrogen. Thus stroke has long been considered as a problem afflicting men, but there is a steep increase in the incidence of stroke in postmenopausal women, possibly linked to falling estrogen levels. It is apparent that the mechanisms underlying differences in cerebrovascular func-
tion between sexes need to be determined to define strategies to prevent pathological events.

In summary, male SHRSP exhibit reduced myogenic adaptation and increased vascular stiffness, which may contribute to cerebral ischemic injury (1, 6, 24). In the long term, these vascular characteristics may elevate cerebral pressure and further augment vascular stiffness by enhancing matrix synthesis. Elucidation of the cellular (endothelial, SM, and adventitial) and molecular mechanisms in myogenic responsiveness, possibly involving genetic factors, is warranted to identify novel therapeutic targets to correct vascular dysfunction and limit cerebrovascular disease.

GRANTS

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