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Commentary

Hypertension is a leading cause of cognitive impairment and dementias. Such loss of brain health has a vascular component, but the mechanisms involved are poorly defined. In this issue of the *JCI*, Koide et al. provide evidence that end-organ effects of hypertension on capillary endothelium and inward-rectifier K^+ channels (Kir2.1) impair integrated propagation of electrical signals and vasodilation upstream, resulting in reduced neurovascular coupling (NVC) despite neural activation. NVC was partly restored by amlodipine, but not losartan. Moreover, NVC was improved by eplerenone in the presence of losartan, suggesting a role for aldosterone. These findings support the concept that endothelial cells and Kir2.1 are potential therapeutic targets to prevent or reverse the loss of NVC and the vascular component of cognitive deficits that occur with increased frequency during hypertension.

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Hypertension-induced reductions in neurovascular coupling

The brain has limited energy reserves. As a result, increases in neural activity are rapidly followed by local increases in cerebral blood flow (CBF), providing oxygen and glucose that support energy demands, while removing metabolites and unwanted molecules. This series of events is commonly described as neurovascular coupling (NVC) or functional hyperemia. In addition to its physiological importance, the hemodynamic component of NVC is the basis for functional magnetic resonance imaging signals, a common approach in brain mapping. Because of its importance as an adaptive response and a clinical tool, defining mechanistic details that underlie NVC has been a goal for many years. By definition, the process is multicellular. It has been studied in diverse regions of the brain and involves multiple cells and segments of the circulation (1, 2). Considering these concepts, it is not surprising that impairment of NVC, which occurs during aging and a variety of disease states, has implications for brain health.

Hypertension is a global pandemic and the leading modifiable cause of vascular disease and premature death (3, 4). The vasculature of the brain is a key target of hypertension, and as a consequence, a major risk factor for cerebrovascular disease, atherosclerosis, stroke, cognitive deficits, and dementias (4–6). In hypertensive humans, NVC is reduced and cognitive impairment is common (Figure 1) (7, 8). While progress has been made in defining mechanisms responsible for hypertension-induced reductions in NVC (Figure 1), the full cell-specific complement of genes, molecules, and networks involved remains to be defined. To date, progress in this area of study is predominantly based on data from preclinical models.

Defining the impact of chronic hypertension

In this issue of the *JCI*, Koide et al. (9) used a recently developed brain capillary-parenchymal arteriolar preparation (10) to help fill this knowledge gap. In previous work, the authors provided evidence that neural activation, with the associated increase in extracellular potassium (K^+), is sensed by capillary endothelia, initiating an endothelial cell Kir2.1–dependent hyperpolarizing signal. This signal spreads to adjacent endothelial cells via gap junctions and finally vascular muscle (via myoendothelial junctions), as it propagates upstream from the site of origin (Figure 1). This physiological orchestration results in an increase in the diameter of parenchymal arterioles, followed by diameter increases in pial arterioles and arteries. Vasodilation of resistance vessels upstream occurs in the absence of changes in the diameter of capillaries themselves (10). Thus, although capillaries are not major resistance vessels (1, 11), they are intimately associated with neurons, functionally integrating changes in neural activity with local perfusion (Figure 1). Because direct imaging of the microcirculation in the human brain currently ranges from difficult to impossible, studies of NVC in humans often take advantage of this propagated response by measuring blood flow changes or other endpoints in larger cerebral arteries (8).

Although treatment in humans that reduces arterial pressure is protective against stroke, effects on cognitive deficits and dementias have been less clear (12–14). Koide et al. sought to better define the impact of chronic hypertension, and treatment of hypertension, on NVC using a mouse model. The authors hoped to gain insight into effects of hypertension on NVC. Further understanding of such mechanisms may support development of new or more effective therapeutic strategies to preserve the integrity of NVC and protect against loss of cognition or other categories of brain function (9).

Koide et al. present several findings (9). Endothelium- and Kir2.1-dependent vasodilation in response to local increases in K^+ ex vivo, or increases in local CBF following somatosensory stimulation in vivo, was impaired in male and female hypertensive mice (the Schlager BPH/2J poly-

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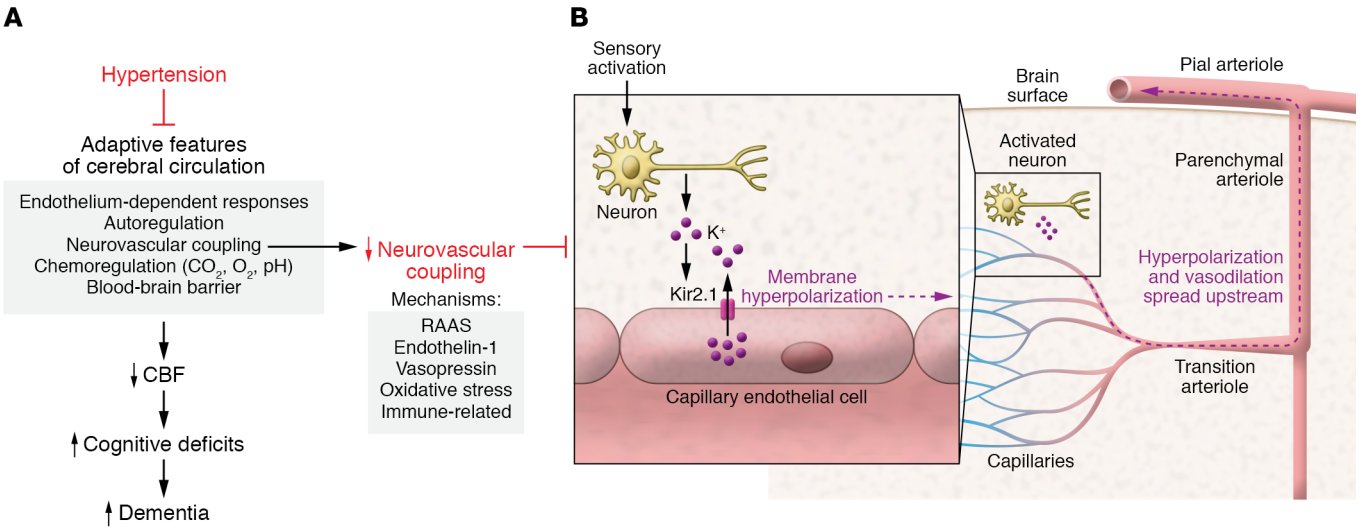

Figure 1. Impact of hypertension on neurovascular coupling. (**A**) Hypertension impacts major adaptive features that contribute to regulation of CBF. Loss of these mechanisms results in reductions in NVC, CBF, development and progression of cognitive deficits, and eventually dementias. (**B**) In normotensive individuals, activated neurons release K^+. Extracellular K^+ activates Kir2.1 channels on capillary endothelial cells to release K^+, resulting in membrane hyperpolarization that spreads upstream from endothelial cells to adjacent endothelial cells as well as to vascular muscle cells. Hyperpolarization of vascular muscle produces vasodilation. CBF, cerebral blood flow; RAAS, renin-angiotensin-aldosterone system; TA, transition arteriole; NVC, neurovascular coupling.

genic strain) compared with normotensive controls (BPN/3J). These effects were partially prevented by administration of amlodipine (an inhibitor of Ca^{2+} channels), but not losartan (an inhibitor of the angiotensin II type 1 receptor [AT1R]), despite similar effects on arterial pressure (measured by tail-cuff plethysmography). The lack of effect of losartan was associated with increased plasma concentrations of aldosterone. Additional studies revealed that an aldosterone receptor antagonist (eplerenone) improved NVC in BPH/2J mice in the presence of losartan. The data collectively confirm that hypertension impairs NVC, while providing insight into mechanisms involved. Further, the findings suggest endothelial Kir2.1 could be a therapeutic target to prevent or reverse the loss of NVC and the vascular component of cognitive impairment or dementias that occur with increased frequency in hypertensive individuals, including those treated with AT1R antagonists.

The Koide et al. study has multiple strengths, including a unique pressurized capillary-arteriolar preparation that provides insight into mechanisms that control myogenic tone of parenchymal and pial arterioles, which are important resistance vessels in the brain. Studies were performed at two time points in both male and female mice with life-long hypertension. Rather than solely relying on an ex vivo model, complementary in vivo experiments were included that examined NVC using a natural stimulus for neural activation. The design included testing effects of three antihypertensive agents, which provide interesting data related to drug class–dependent effects as well as a role for aldosterone in mechanisms that impair NVC. Lastly, the researchers revealed mechanisms that affect capillary endothelial cells and contribute to a loss of NVC during hypertension.

There were also a few limitations. First, cognitive studies were excluded from the mouse evaluation, so the functional impact of impaired NVC in relation to brain function during hypertension is not entirely clear. For example, although amlodipine improved NVC in BPH/2J mice, recent findings from hypertensive humans indicate that the same inhibitor had no measurable effect on the long-term incidence of dementia, although it was effective in prevention of stroke (14). Second, the lack of effect of losartan on NVC during hypertension is somewhat surprising. Although specific details differ, part of the current results contrast with previous findings regarding the role of the AT1R and effects of losartan on NVC in both an angiotensin II–induced model of hypertension and BPH/2J mice (15, 16). Third, in relation to interpretation, the genetic and mechanistic basis for hypertension in BPH/2J mice is ill defined. There is likely a neurogenic component, but specific details remain lacking or are quite complex (17). Thus, what mechanism or contributor to human hypertension is modeled by this mouse strain is not entirely clear.

Conclusions and questions

Brain health is dependent on vascular health. It is clear in both preclinical models and humans that hypertension is one of the greatest risk factors for large and small vessel disease. Cerebrovascular disease causes cognitive deficits (Figure 1) much more often than classic clinical stroke (18). All major dementias have a substantial vascular component (19, 20). Some experts stress that the vascular component of cognitive deficits and dementias represents the only major treatable component of these processes at this time (19, 20). To eventually develop more effective therapies for cerebrovascular disease, we need to better understand brain vascular biology under normal conditions and in the presence of leading risk factors such as hypertension.

Future discoveries in this area of study may benefit from several lines of

investigation. First, is the endothelium- and Kir2.1-dependent component of NVC impaired in other models of hypertension and in the brain of humans with hypertension? Second, is this mechanism unique to the somatosensory cortex, or is it present in other regions that exhibit NVC (i.e., the visual, auditory, and olfactory cortex; the hippocampus or cerebellum)? Is it present and affected by hypertension in both gray and white matter? Third, the potential contribution of aldosterone to impaired NVC has received little attention previously. The findings from Koide et al. (9) are interesting in relation to the role of mineralocorticoid receptors in forms of human hypertension (i.e., primary hyperaldosteronism, individuals with resistant hypertension, etc.) (21). At this point, it is unclear if increases in plasma aldosterone produce similar effects on NVC in the absence of losartan. A different model revealed that chronic administration of aldosterone impaired other aspects of endothelial function in the cerebral circulation via oxidative stress (22). Finally, previous studies have highlighted other mechanisms as contributors to loss of NVC in models of hypertension (Figure 1). These include angiotensin II and the AT1R, reactive oxygen species and NADPH oxidase, and immune-related mechanisms involving perivascular macrophages (Figure 1) (2, 12, 13, 23). Future studies to determine how the current findings and mechanisms integrate with or complement these previously described may allow clinicians to better individualize treatment for patients with hypertension while minimizing the risk for cognitive impairment.

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