Heart failure (HF) is characterized by an enhanced neurohumoral drive, which is currently the major therapeutic target. Recent studies to explore the mechanisms involved in central sympathetic outflow in HF have revealed several candidate mechanisms, such as reduced NO activity, increased oxidative stress, and activation of the brain angiotensin-aldosterone system. Interactions between these complex factors may also induce transcription factor alterations and increase sympathetic nervous system activity.

The article in the present issue of Hypertension by Yu et al describes a very interesting concept that peripheral macrophages mediate central sympathetic activation after myocardial infarction (MI). Kang et al suggested previously that cyclooxygenase-2 (COX-2) and the subsequently generated prostaglandin E2 (PGE2), which crosses the blood-brain barrier, increase sympathetic activity. In this study, Yu et al injected clodronate liposomes intracerebroventricularly into rats 24 hours after inducing acute MI to selectively eliminate MI-induced brain perivascular macrophages. Because the effects of the clodronate liposomes peak ~1 week after injection, COX-2 immunoreactivity in perivascular macrophages and COX-2 mRNA and protein levels were evaluated 1 week later. Perivascular macrophages in the blood-brain barrier were successfully eliminated in rats treated with clodronate liposomes; as a result, COX-2 immunoreactivity was not observed, and PGE2 in the cerebrospinal fluid was reduced. The authors suggest that these phenomena reduced central sympathetic outflow, as evaluated by plasma norepinephrine concentration.

Yu et al also focused on the importance of the activity of the paraventricular nucleus of the hypothalamus (PVN) leading to enhanced central sympathetic outflow in HF. For this purpose, they examined Fos-related antigen-like immunoreactivity, which is a marker of chronic neuronal activation. In another protocol, they injected tumor necrosis factor (TNF)-α into a carotid artery in normal rats. As expected, injection of TNF-α into the carotid artery increased renal sympathetic nerve activity, mean arterial blood pressure, and heart rate.

These responses were significantly attenuated in rats treated with clodronate 1 week before the intracarotid TNF-α injection. In addition, clodronate treatment blocked the TNF-α–induced increases in perivascular macrophages and COX-2 immunoreactivity and attenuated cerebrospinal fluid PGE2 concentrations. Their findings strongly support their attractive hypothesis that proinflammatory cytokines, such as TNF-α, increase the number of brain perivascular macrophages, thereby activating COX-2 and generating PGE2, which leads to sympathoexcitation in rats after MI as a model of HF.

Circumventricular organs, such as the organum vasculosum of the lamina terminalis, a hypothalamic area that lacks a blood-brain barrier, are considered to be important sites of action of circulating cytokines. In addition, the anterior wall of the third ventricle has a high density of PGE2 binding sites. These areas also have abundant angiotensin II type 1 receptors and are related to central blood pressure control. Yu et al focused on the role of the PVN and the suggested mechanism might be related to this forebrain area. In addition, it is well established that the rostral ventrolateral medulla (RVLM) is involved in the enhanced central sympathetic outflow in HF. Reduced NO, increased oxidative stress, and activation of angiotensin II type 1 receptors in the RVLM all contribute to sympathetic drive. Therefore, it will be important to examine whether a similar mechanism is involved in other major autonomic nuclei in the brain, such as the RVLM, and whether the PVN-RVLM axis plays an important role in sympathoexcitation in HF. There may be some interaction between cytokine generation and the autonomic nervous system. In addition, although Yu et al did not find a role for microglia based on the clodronate treatment, it is important to examine whether microglia that are activated in HF or by inflammation also play a role in sympathoexcitation.

As the authors mention, inflammation has a pivotal role in cardiovascular diseases, including HF, MI, hypertension, and diabetes mellitus. This concept in acute MI is relatively easy to accept. The ischemic heart produces cytokines, which then circulate in the bloodstream. Circulating cytokines, such as TNF-α and interleukin-1β, increase after MI, thereby increasing the number of perivascular macrophages in the endothelium, which leads to COX-2 expression. Recent studies, however, suggest that, even in very early stage cardiovascular disease, risk factors for cardiovascular disease, such as hypertension, hypercholesterolemia, and/or diabetes mellitus, induce inflammation of the vasculature and/or target organs. Yu et al...
suggest an important mechanistic possibility that brain perivascular macrophages increase COX-2 expression, and the resulting generation of PGE2 could be a key player in central sympathetic activation in chronic HF, hypertension, or diabetes mellitus. Sympathetic cardiovascular activation is clearly involved in human hypertension, including stages, clinical forms, patterns of 24-hour blood pressure, end-organ damage, and metabolic abnormalities. Thus, the mechanism suggested by Yu et al.4 might be active even when the blood-brain barrier is intact, although because the endothelium may also be an important component of the blood-brain barrier, the barrier function could be diminished. It would be interesting to examine the role of perivascular macrophages in the effects of factors such as angiotensin II, NO, and oxidative stress, which are well established to be involved in central sympathetic outflow in HF. Finally, it will be important to examine the extent to which this suggested mechanism is responsible for the enhanced central sympathetic drive in HF and how this finding can be translated to a treatment for HF. In summary, Yu et al.4 show a novel mechanistic insight into the interaction between the heart and brain via neurovascular coupling (Figure).

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