Brain Mechanisms Contributing to Sympathetic Hyperactivity and Heart Failure

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It is well recognized that the initial myocardial injury and associated decrease in left ventricular (LV) function activate progressively a variety of systems, which in the long-term contribute to progressive cardiac dysfunction and clinical heart failure. Studies on the pathophysiology of the CHF syndrome have extensively focused on the activity of systems such as the sympathetic nervous system (SNS) or the renin-angiotensin-aldosterone system (RAAS) and their effects on the heart. From a therapeutic perspective, activation of the different mechanisms is generally considered to occur independent of each other, resulting in the current polypharmacy approach to CHF. Current interventional approaches counter only the peripheral effects of increased sympathetic drive by \( \beta \)-blockers. The latter approach does not inhibit the sympathetic hyperactivity per se and effects mediated via e.g., \( \alpha \)-receptors in the heart, kidneys and blood vessels. Much less is known about the determinants of the activation of the SNS or the RAAS, to prevent their activation and thereby their contribution to progressive cardiac remodeling and dysfunction. In this regard, it is essential to know whether the contributing mechanisms are activated in a coordinated fashion. In this case strategies can focus on maintaining normal activity in this coordinating center, and one may envision that 1 (or 2) interventions may be sufficient. In recent years it is becoming apparent that the CNS may act as the conductor integrating input from a variety of sources in the body which leads to activation of CNS mechanisms whose peripheral output plays a major role in progressive cardiac remodeling and dysfunction (Figure). Studies providing the “proof of concept” were performed in transgenic rats expressing an antisense RNA against angiotensinogen mRNA specifically in the brain resulting in enhanced pro-inflammatory mediators in the CNS. The authors concluded that post MI in the CNS MR activation increases ENaC activity, thereby causes “ouabain” release possibly from magnocellular neurons in SON and PVN and “ouabain” somehow causes increased AT1-receptor stimulation in the PVN.

From a mechanism perspective, such central infusions have been shown to affect a variety of peripheral mechanisms which may contribute to progressive cardiac dysfunction such as prevention of sympathetic hyperactivity, of activation of the circulatory and cardiac RAAS and of increases in plasma TNF-\( \alpha \) and possibly vasopressin levels.

Altogether, the above findings strongly support the concept that a single intervention to prevent increased activity in CNS pathways post MI can be remarkably effective to prevent activation of several peripheral mechanisms and thereby a major component of cardiac dysfunction post MI.

It has not yet been clarified how the initial cardiac injury would activate these CNS pathways and how in the CNS these different factors interact. Several mechanisms may contribute to activation of CNS pathways post MI. First, post MI, cardiac vagal or sympathetic afferent fibers conveying mechanosensitive and chemosensitive information to the CNS are activated and through AT1-receptors in the PVN, contribute to sympathetic excitation. Secondly, post MI the circulatory RAAS becomes rapidly activated by e.g., a decrease in the blood pressure. Both Ang II and aldosterone may activate CNS pathways leading to sympathetic hyperactivity. Recent studies by Felder’s group suggest as a third mechanism that increased levels of circulating cytokines post MI cause induction of COX-2 expression in the microvasculature of the PVN resulting in enhanced pro-inflammatory cytokines in the PVN and sympatho-excitation. The authors did not address whether this mechanism is specific for the PVN or also occurs in other nuclei activated post MI such as the SON and the locus ceruleus. Oral treatment with a MR antagonist or an anti-cytokine agent alone or combined for 6 weeks post MI similarly blunted the increases in plasma cytokines, COX-2 staining in small vessels in the PVN region, as well as blunted neuronal and cytokine activation in the PVN and the increase in plasma NE but not in plasma aldosterone. The authors concluded that an orally administered MR antagonist lowers circulating cytokines post MI, and thereby reduces cytokine-induced expression of inflammatory and sympatho-excitatory mediators in the CNS. The MR blocker crosses the blood-brain barrier and its central infusion prevents increases in both sympathetic activity and plasma cytokines post MI. Central MR blockade may therefore have played a major role in decreasing cytokine levels in...
the PVN and as a result or in parallel decreased sympathetic outflow.

In a follow-up study published in the current issue of *Circulation Research*,12 Felder et al directly assessed the role of cytokines in the CNS by overexpressing a potent anti-inflammatory cytokine, interleukin (IL)-10. CNS studies again focused on the PVN. However, some parameters were assessed in the whole hypothalamus and observed changes likely reflect changes in other regions of the hypothalamus as well. One week after central gene transfer, ie, at 2 weeks post MI, activity of pro-inflammatory cytokines in the hypothalamus or PVN was similarly decreased as in the first study, and the marked increase in plasma NE attenuated. Both studies also measured parameters of cardiac remodeling and dysfunction. In the chronic study,10 the marked increase in LVEDP (up to 26 mm Hg) was modestly attenuated (down to 18 mm Hg). Other parameters of LV function such as dP/dt\(_\text{max}\) were not reported. As assessed by echo, no effects at all were noted on progressive LV dilation and decrease in ejection fraction after 6 weeks of treatment. In contrast, the increase in RV weight was fully prevented. In the current study, the <1 week treatment markedly blunted the increase in LVEDP (21 versus only 9 mm Hg). The decrease in LV dP/dt\(_\text{max}\) was also partially prevented as was the increase in RV weight. Unfortunately, in this study no follow-up echo was included to assess whether the much lower LVEDP was associated with less LV dilation and the better dP/dt\(_\text{max}\) with eg, improved ejection fraction. The authors explain these cardiac findings by “a significant reduction in preload related to increased sodium and water excretion could explain these early findings”. Although such an effect of lower renal sympathetic tone likely contributes, decreased sympathetic activity to the splanchnic capacitance bed decreasing venous return13 may be as important, as well as a presumably better LV pump function. A lower preload may actually lower dP/dt\(_\text{max}\) rather than causing an increase. Instead the central anti-inflammatory response may have inhibited early mechanisms contributing to myocyte loss and decreased myocyte function.

The authors do not attempt to compare the effects on cardiac function in the 2 studies or with other studies. The oral MR blocker and the central IL-10 treatment appeared to similarly blunt the activation of the central mechanisms involved in progressive cardiac dysfunction. Both studies used rats with very large MIs (up to 50% of LV circumference) and marked increases in LVEDP. Both studies used pentobarbital anesthesia to measure LV function and collect blood samples for plasma NE. The autonomic and cardiac effects of this barbiturate may have varied depending on the treatments used and affected the results in an unpredictable manner. Nonetheless, comparison of the findings in the 2 studies may indicate that central cytokine suppression is initially quite effective in lowering preload and improving LV systolic function, but this effect may diminish over time. More effective blockade of these central mechanisms by direct central infusions of a MR blocker or AT\(_1\)-receptor blocker as compared with the blunting only caused by the (low-dose) oral MR blocker may also explain the marked attenuation of LV remodeling with the central RAAS blockade.3,4,5 In addition, it is possible that central mechanisms have less influence on chronic cardiac remodeling after large MI’s as used by Felder’s group. Following moderate size MI cardiac remodeling and dysfunction develop more gradually.

Irrespective of some of the limitations, the present study by Felder’s group clearly demonstrates that the increase in proinflammatory cytokines in the brain post MI is not just an epiphenomenon. They appear, at least in the short term, to contribute to sympathetic hyperactivity and cardiac dysfunction. Further studies are clearly needed to assess how increased cytokine activity relates to the activation of the brain RAAS or “ouabain” post MI. One may speculate that these cytokines act as amplifiers and therefore their blockade is not as effective as central RAAS blockade. From a therapeutic perspective it is increasingly clear that targeting one of the steps in the CNS pathways is a rather effective strategy in blunting progressive cardiac remodeling and dysfunction post MI. It will be crucial to assess blockade of which of the steps provides the most benefits and the least adverse effects, and whether benefits of central blockades initiated early post MI (“prevention”) also can be seen if central blockades are initiated once CHF has developed.
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Disclosures

None.

References

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