

## Commentary

### WHAT'S NEW IN SHOCK, FEBRUARY 2008?

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The articles in this month's edition of *SHOCK* invoke several common themes, including endotoxin-elicited proinflammatory and anti-inflammatory mechanisms, as well as organ-specific responses to I/R, hypoxia, and extreme stressors. Several observations are notable, including two divergent observations of intercellular adhesion molecule (ICAM) expression and its relationship to anti-inflammatory status. Hamano and colleagues (1) extend their observations of reduced ICAM-1 expression in relationship to adenosine receptor activation. They note that adenosine A2A engagement reduced ICAM-1 expression and tumor necrosis factor- $\alpha$  production partially independent of A2A stimulation of cAMP. Walsh and his coinvestigators (2) also noted diminished ICAM-1 expression in human umbilical vein endothelial cells during blockade of the exportin-1 pathway. This pathway is important for shuttling of RelA/I $\kappa$ B- $\alpha$  between cytoplasm and nuclear sites and is proposed as a mechanism for partial control of nuclear factor- $\kappa$ B transcription activation of proinflammatory signals.

Lendemans and colleagues (3) have used an *in vivo* endotoxin-tolerant model to investigate leukocyte adherence and capillary leakage in the mesenteric microcirculation. Somewhat counterintuitively, they observed increased polymorphonuclear leukocyte adherence in postsinusoidal and mesenteric postcapillary venules after a second LPS challenge. The protective effects of endotoxin tolerance therefore seem independent of adherence at these sites.

Arginine vasopressin promotes several protective responses during endotoxemia, including maintenance of systemic blood pressure and renal perfusion. It is unknown if one mechanism for maintained urinary flow and sodium resorption is from restoration of apical aquaporin 2 activity. Versteilen and her associates (4) used the arginine vasopressin-V2 receptor agonist, desmopressin, to address this issue in rodents and observed that this agent increased sodium resorption without altering the localization of aquaporin 2.

As has been frequently discussed in these pages, the systemic response to endotoxin may vary depending upon factors including the total dose and timing of ligand administration. This has been reconfirmed in a porcine model by Lipcsey and colleagues (5), who noted that more rapid administration of a fixed LPS dose resulted in enhanced proinflammatory responses.

Yilmaz and colleagues (6) provide us with an intriguing investigation into the role of the preoptic anterior hypothalamic area regulation of LPS-induced hypotension. Under the hypothesis that afferent vagal signals emanating to the preoptic anterior hypothalamic area may result in both an early transient and later sustained phase of hypotension, they blocked neuronal signaling in this region and observed a reduction in the hypotension resulting from LPS challenge. Interestingly, they observed a concomitant reduction in tumor necrosis factor- $\alpha$  levels after LPS. I commend this article to the reader for the many fascinating questions it evokes regarding evolving concepts of central nervous system regulation of inflammatory responses.

A variation of the LPS toxicity theme relevant to husbandry readers is the report of Kuckleberg and his associates (7) who investigated the effects of the common bovine coccobacillus, *Histophilus somni*, which causes a thrombotic disease in cattle. Endotoxin derived from this pathogen activates platelets, and they have demonstrated that this also leads to expression of several ligands on endothelial cells (ECs). Importantly, they also made the unique observation that ECs seem to engulf these activated platelets. The implications of this finding across species are unknown at present.

Zhan and colleagues (8) have observed the increased expression of LPS binding protein/CD14 and high mobility group box 1 in a cecal ligation and puncture rodent model. They have also confirmed that a bactericidal permeability increasing protein, rBPI21, limits these expression patterns and organ injury, as well as improving survival. This influence of rBPI21 in chronic models of injury is consistent with current thinking related to latent inflammatory mediator activities.

Other unanticipated findings resulting from the use of an immunoglobulin M-enriched solution during endotoxemia were noted by Stehr and associates (9). After live *Escherichia coli* infusion, they observed that this solution seems to increase *in vivo* phagocytosis of polymorphonuclear leukocytes, improve lung histology, and reduce colony counts in liver and spleen of rabbits.

Although the serine-threonine phosphatase, PP2A, has been demonstrated to associate with *c-Jun* N-terminal kinase, the upstream signaling effects of this molecule are not known. Zhao and colleagues (10) have noted that PP2A exhibits interactions with the regulatory kinases MAP/Erk kinase kinase 1 and MAP kinase kinase-4 in THP-1 cells. This finding has implications for regulation of the overall proinflammatory phenotype.

The report of Cusher and his associates (11) provides another twist to the proposed mechanisms of cellular protection afforded by tight glucose control. Using an *in vitro* model of endotoxin exposure, they observed that insulin treatment resulted in diminished I $\kappa$ B degradation and increased SH2-containing inositol 5'-phosphatase activity.

Several traditional medicines have been used for their anti-inflammatory properties, among them *Salvia miltiorrhiza*, of which the active soluble components include dihydroxyphenyl lactic acid (DLA) and salvianolic acid B (SAB). Guo and colleagues (12) have investigated the post-LPS effects of DLA and SAB in rat mesenteric vessels by determining parameters of flow and markers of EC activation. They observed that DLA and SAB improved microcirculatory flow and inhibited local tissue inflammatory signals.

Enhanced tissue EC activation was also evaluated in a prolonged hemorrhagic rodent shock (HS) model by Van Meurs and associates (13). They noted not only that induction of inflammatory gene expression develops during the hypotensive phase, but also that HS was not associated with induction of hypoxia-responsive genes (i.e., hypoxia-inducible factor-1 $\alpha$  and vascular endothelial growth factor-A). The surgical stress associated with instrumentation in the model was sufficient to induce EC activation status. This later observation is consistent with a growing body of evidence that initial sterile stress may dominate much of the subsequent inflammatory consequences in these models.

Chen and colleagues (14) assessed the influence of early L-arginine administration on brain cerebrovascular function after heatstroke. This agent not only reduced intracranial hypertension, but also reduced the expression of many mediators and inducible metabolites associated with this injury.

Several articles in this edition have focused upon intestinal tissue responses to I/R injury. Among these is a report of Costantino and associates (15) who addressed the contribution of the Jak-STAT signaling pathway during I/R. They demonstrate that Jak-/- and STAT1-/- animals exhibit not only reduced intestinal epithelial cell destruction but also diminished expression of matrix metalloproteinases (2, 9, 14) and adhesion molecules (ICAM-1 and P-selectin). Inoue and colleagues (16) investigated the expression of heme-oxygenase-1 (HO-1) in various segments of intestine after HS. They demonstrate the segment-specific expression and protein appearance of HO-1 and differential induction of HO-1 during resuscitation.

Several studies have also assessed organ responses to preconditioning stressors including the repeat intestinal ischemia studies performed in swine by Solligard and his associates (17). Animals received either a single or repeated superior mesenteric artery cross-clamping followed by reperfusion. They note a lesser biochemical and permeability response during the second period of I/R. In a very interesting study, Chen and colleagues (18) have used isoflurane anesthetic preconditioning to assess responses to subsequent cardiac I/R, noting decreased cardiac O<sub>2</sub><sup>-</sup>, increased adenosine triphosphate content, and increased manganese superoxide dismutase activity. They postulate that anesthetic preconditioning-induced O<sub>2</sub><sup>-</sup> effects on mitochondrial K<sub>ATP</sub> channel function

may contribute to this benefit. Ghuysen and colleagues (19) have investigated the influence of right ventricular (RV) performance in a model of progressive outflow resistance with a model of repeated pulmonary emboli. They observed decreased RV stroke volume decreases associated with RV vascular uncoupling. The physicochemical basis for this uncoupling remains to be determined.

Obaid and coinvestigators (20) have assessed the relative hemodynamic effects of epinephrine and dopamine after hypoxia in piglets. The administration of these agents after the onset of reoxygenation resulted in only modest differential indices of cardiac performance and systemic hemodynamics.

Finally, Tulley and her colleagues (21) have investigated the role of the invariant natural killer T-cell (iNKT) subset (V $\alpha$ 14-J $\alpha$ 281) in a murine burn model to determine the influence of this receptor on injury-induced suppression of T-cell immunity. Administration of  $\alpha$ -galactosylceramide, a synthetic glycolipid presented to NKT cells by CD1d molecules, is known to promote immunity in viral, mycobacterial, and cancer models. Treatment with this agent in this injury model prevented burn-induced suppression of delayed-type hypersensitivity, T-cell proliferation, and interferon- $\gamma$  production. These studies support a role for iNKT cells in injury-induced immunosuppression. Although late outcome was not assessed, the study also supports the concept of acute targeting of such cells in the management of severe injury.

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