This is the Fourth article in the Journal's series on major trauma. Chaudry and Bland, leading experts in the field, consider the cellular implications of injury.

Leading article

Cellular mechanisms of injury after major trauma

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Protracted reduction in tissue perfusion after major trauma (henceforth referred to as trauma) in an individual produces profound effects on tissue metabolism, structure and function. This is apparent at cellular, organ and systemic levels[1,2]. Major changes after trauma occur in the microcirculation, cell membrane transport and function, energy metabolism, and function of mitochondrial, immunological and cardiovascular systems. With continued hypoxia/ischaemia and sludging of blood[1], parenchymal and endothelial cells are likely to swell[1–3], preventing rapid return of normal blood flow after fluid resuscitation.

Low-flow conditions of trauma have a profound impact on mitochondrial function. Mitochondria generate around 95 per cent of the body's energy requirements, making them the focus of many trauma studies, which mostly centre on dysfunction arising via signals from hypoxia[1–3]. The harbinger of mitochondrial failure is the opening of permeability transition pores and megapores[2]. Pore opening permits leakage of ions, metabolites and macromolecules, causing mitochondrial swelling and membrane depolarization. Further mitochondrial damage can come from the actions of proteolytic enzymes and reactive oxygen species[1–3], adding insult to membrane integrity and electron potential. Whether mitochondria recover or not after trauma makes them an effective 'mine canary' relative to the organism's survival.

Mitochondrial dysfunction in shock also has ripple effects for substrate utilization, altered cation contents, decreased adenine nucleotide trans locase activity, increased free fatty acids/decreased metabolic capacity, and apoptosis[1–4]. Cell membrane transport of cations, transmembrane potential, cellular adenine nucleotide levels, signal transduction and cyclic nucleotides are also altered[1,3]. This is reflected in decreased myocardial contractility, cardiac output, hepatocellular and endothelial cell function, and gut absorptive capacity at the organ level[1–3,5]. These changes occur experimentally in male rodents during and after trauma, and in pro-oestrus females during shock; however, most revert to normal in pro-oestrus females after resuscitation[2,3]. In addition, blood volume restitution following trauma occurs more rapidly and may be a major mechanism responsible for the protection of pro-oestrus females under those conditions[2,3].

T and B cell functions are also depressed in male mice and humans after trauma[2,6]. Antigen presentating capacity is depressed in all macrophages, dendritic cells and keratinocytes from different body compartments; only Kupffer cells are upregulated to produce proinflammatory cytokines[2].

The endocrine, immune and neural systems are part of a complex network closely involved in maintaining body homoeostasis. Numerous experimental studies suggest that cytokines mediate the changes that follow trauma[2,3,6–8]. Clinical evidence of interaction between the immune system and the hypothalamic–pituitary–gonadal axis is based on sexual dimorphism. This is exemplified in the higher prevalence of autoimmune diseases in women and altered immune responses during pregnancy, events not typically associated with trauma. The effects of 17β-oestradiol, 5α-dihydrotestosterone (DHT) and progesterone are evident not only on immune cells but also on endothelial cells, cardiac myocytes and hepatocytes[2,3,8]. Local production of these steroids in addition to systemic sex steroids plays an important role in regulating cellular functions[2,3]. Studies have also shown major differences in cytokine production after experimental trauma between male and pro-oestrus female mice, and divergent effects of male and female sex steroids on cytokine production[2,3]. Furthermore, increased susceptibility to sepsis following trauma is observed in males but not in pro-oestrus females[2,3].

Sexual dimorphism in cardiovascular and immune responses (mediated by sex steroids) has focused attention on the role of 17β-oestradiol and DHT as primary mediators of sex differences. Sex steroids also act directly on the immune system by modulating T lymphocytes and macrophage activation, and cytokine gene expression. Oestrogen and androgen receptor expression on

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various cells[8] indicates direct communication between immune, cardio vascular, endocrine and central nervous systems. Additionally, sex steroids modulate the hypothalamic–pituitary–adrenal axis[2]. However, interaction between this axis, sex hormones, genetic factors and the immune system is complex; many factors must be considered when studying the effects of sex differences following trauma. Collectively, these factors affect immune responses through modulation of cytokine production and effector cell function. The nature of the antigen and character of the immune response (T helper cells type 1 and 2) determine the outcome of immune response following trauma.

Although significant research has been conducted on sex differences in immune function, more effort is needed to understand the role sexual dimorphism plays from the early development of immunity (for example lymphoid and myeloid cell maturation) to the mature organism's ability to process and respond to challenges (innate or adaptive immunity)[2,3,6]. Variations between pattern recognition and subsequent responses to pathogens (or endo genous stimuli) by male and female innate immune systems should be investigated. Within the adaptive immune system processes such as cellular element developmental variations, antigen processing and presentation, cytokine production, tolerance induction and regulatory influences may likewise reveal important distinctions attributable to sex that could come to play in the context of injury.

Future research priorities should be those that correct or modulate perturbed cellular and sub cellular alterations. In the area of sex differences[2,3,8–10], mechanisms by which the primary sex hormones, oestradiol and DHT, affect immune and cardiovascular function should be examined. Furthermore, a greater understanding of the effects of naturally fluctuating hormone concentrations on immune and cardiovascular responses is needed. The contributions of carbon monoxide, nitric oxide, endoplasmic reticulum stress proteins, hypoxia inducible factor 1α, chemokines, proinflammatory and anti-inflammatory cytokines, and various oestrogen receptors on cell surface and cytoplasmic and nuclear locations after trauma should be investigated. Stem cell use as an adjunct to resuscitation should also be explored. Significant differences in outcome after trauma in pro-oestrus females, and in young and aged male mice, provide an opportunity to follow disease-relevant immune and cardiovascular responses over a relatively short time period. It is also important to focus on the interplay between hormone systems, particularly sex steroids and stress steroids (corticotrophin releasing hormone and cortisol), because both profoundly affect immune and cardiovascular responses. The possibility of using sex hormones to modulate these responses during the management of trauma is a promising area of investigation. Such intervention might reduce morbidity and increase survival after trauma.

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References

1 Chaudry IH. Cellular mechanisms in shock and ischemia and their correction. *Am J Physiol* 1983; **245**: R117–R134.
2 Hasselgren P-O, Hubbard WJ, Chaudry IH. Metabolic and inflammatory responses to trauma and infection. In *Mastery of Surgery* (5th edn), Fischer JE, Bland KI (eds). Lippincott Williams & Wilkins: Philadelphia, 2007; 2–24.
3 Hsieh Y-C, Frink M, Choudhry MA, Bland KI, Chaudry IH. Metabolic modulators following trauma/sepsis: sex hormones. *Crit Care Med* 2008; **35**(Suppl): S621–S629.
4 Brahmamdam P, Watanabe E, Unsinger J, Chang KC, Schierding W, Hoekzema AS *et al*. Targeted delivery of siRNA to cell death proteins in sepsis. *Shock* 2009; **32**: 131–139.
5 Deitch EA, Senthil M, Brown M, Caputo F, Watkins A, Anjaria D *et al*. Trauma-shock-induced gut injury and the production of biologically active intestinal lymph is abrogated by castration in a large animal porcine model. *Shock* 2008; **30**: 135–141.
6 MacConmara MP, Maung AA, Fujimi S, McKenna AM, Delisle A, Lapchak PH *et al*. Increased CD4+ CD25+ T regulatory cell activity in trauma patients depresses protective Th1 immunity. *Ann Surg* 2006; **244**: 514–523.
7 Sperry JL, Friese RS, Frankel HL, West MA, Cuschieri J, Moore EE *et al*. Male gender is associated with excessive IL-6 expression following severe injury. *J Trauma* 2008; **64**: 572–578.
8 Yu H-P, Chaudry IH. The role of estrogen and receptor agonists in maintaining organ function after trauma-hemorrhage. *Shock* 2009; **31**: 227–237.
9 Mofidi R, Goldie VJ, Kelman J, Dawson AR, Murie JA, Chalmers RT. Influence of sex on expansion rate of abdominal aortic aneurysms. *Br J Surg* 2007; **94**: 310–314.
10 Zeller CN, Wang Y, Markel TA, Weil B, Abarbanell A, Herrmann JL *et al*. Role of tumor necrosis factor receptor 1 in sex differences of stem cell mediated cardioprotection. *Ann Thorac Surg* 2009; **87**: 812–819.

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