Estrogen increases protective proteins following trauma and hemorrhage

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IN AN EXQUISITELY COMPLETE series of experiments reported in this issue of American Journal of Physiology–Regulatory, Integrative and Comparative Physiology, Dr. Irshad Chaudry’s group has brought us one step closer to understanding the mystery that is estrogen (7). It is not surprising to me that this lab has once again made a leading discovery in trauma-resuscitation science. As the recent recipient of the American Heart Association’s Lifetime Achievement Award for Trauma Science, Dr. Chaudry has devoted the past several decades of his research efforts to the pursuit of understanding and preventing trauma-hemorrhage-induced immune dysfunction, a clinical problem that claims hundreds of thousands of human lives per year in this country. For the past 10 years, Dr. Chaudry’s lab has focused on better understanding the effects of gender and sex hormones on immune dysfunction following various traumatic conditions (12). The group’s progress has been remarkable, and as can be seen by their remarkable article in this issue of the Journal (7), these new findings have brought us very close to harnessing estrogen’s protective mechanisms in the treatment of trauma and hemorrhage.

We have heard a great deal about the protective role that estrogen may play in cardiovascular disease (4–6, 9, 10), but to learn that it protects cardiac and liver function following trauma-hemorrhage (in otherwise nondiseased hearts) is truly “outside the box.” Furthermore, the fact that estradiol does so by increasing other long-appreciated endogenous protective proteins, such as the heat shock proteins that Dr. Chaudry’s group demonstrates in this issue of the Journal, is another important link that allows a significant fast-forward for the field. Translating these findings to the clinical arena will be the next important challenge. Defining the appropriate population, as well as refining treatment to avoid untoward hormonal effects, adds complexity to that challenge. In this regard, translating the basic animal studies (where results appear consistent) to the clinical arena (where the results appear inconsistent) will be the focus of the remainder of this discussion.

Gender differences have been noted in outcome to acute injuries like myocardial infarction, burns, trauma, and sepsis. Hospital-based clinical studies have shown that women have a higher mortality rate after myocardial infarction compared with men (4). In general, the women in many of these studies were older, had higher risk factors (diabetes, hypertension, and congestive heart failure), more complications, and lower likelihood of receiving treatment (8). Importantly, more men died from myocardial infarction before reaching the hospital and the 28-day mortality for men and women was the same (4). This actually suggests that women are relatively protected in the immediate aftermath of a myocardial infarction but are similar to men at the end of a month.

Sepsis and trauma are two other inflammatory conditions associated with gender-dependent outcomes. For mortality in trauma, there is either no gender difference (4) or gender difference in blunt trauma but not in penetrating trauma (4). Studies that have found gender differences are inconsistent. Some studies showed benefit only in women >50 years of age (4), whereas others showed benefit only in women <50 years old (4). Women, however, have lower incidence of pneumonia, sepsis, and multiorgan failure after trauma (4). In sepsis, some studies have found a higher mortality rate in women >80 years old, whereas others have found lower mortality rates for women (4). In a study by Schroeder and colleagues (reviewed in reference 4) involving septic patients, women demonstrated lower mortality and higher IL-10 and lower TNF-α levels. Fewer female patients in intensive care units developed sepsis, although, once sepsis developed, the mortality rate was the same for men and women (11). Clinical studies on gender differences in mortality after burns present inconsistent evidence. Some studies showed women or only women ages 30–59 years old to have higher mortality, whereas other studies showed that women have a lower incidence of multiorgan dysfunction and sepsis after burns (4).

In contrast to the clinical studies, animal studies have consistently found that females do better. Protective effects of acute administration of estrogen, in an in vivo left anterior descending (LAD) coronary artery ischemia-reperfusion (I/R) model, have been shown in different animals (4). Chronic administration of estrogen provides protection from I/R injury in isolated hearts undergoing global ischemia and in hearts undergoing in vivo LAD obstruction. Estrogen also protected against reperfusion-induced arrhythmias after LAD I/R injury. Ovariectomized females have worse cardiac functional recovery after global I/R, in an isolated heart, than sham ovarietomized females or ovariectomized females with estradiol. After burn injury, females have lower cytokine production and better cardiac function. Trauma-hemorrhage leads to depressed immune function and this depression is more severe in males (3, 12, 13). The immune depression is, in part, caused by testosterone (1, 2), because both castration and receptor blockade attenuated this depression. Estrogen also prevented the immune depression caused by trauma-hemorrhage.

Animal studies have consistently shown that females are protected against acute injury while clinical studies appear inconsistent. A possible reason is that in animal studies, the female population is well controlled and only proestrus females are used, whereas clinical studies have a heterogeneous population. Furthermore, the underlying condition of humans is less uniform. Indeed, the few animal studies that used diestrous females showed that diestrous females had functional recovery equivalent to males, but lower than proestrus females. This has been borne out by a few clinical studies that showed cardiac function fluctuates with the hormonal changes of menstrual cycle. Thus it is impor-
tant to know the hormonal status of females and future clinical studies that take this into account may produce more consistent results.

One of the incredibly novel aspects of the present study (7) relates to the rapid signaling and complete processing that must have occurred. In this regard, nuclear transcription and extracellular signaling pathways may be regulated by conventional steroid receptors (SR), such as the alpha and beta estrogen receptors. We now appreciate that SRs may affect signaling by two distinct paths: 1) the nuclear transcription path, whereby activated SRs undergo conformational changes, allowing nuclear translocation, and bind to steroid response elements (SREs) of target genes; and 2) the cytoplasmic or cell membrane signaling (mSR) path, whereby the activated SR influences cytoplasmic signaling processes, which then modulate gene transcription by three potential MAPK-mediated mechanisms. mSR mechanisms as marked by the numbered, blue bullets in the figure: 1) activated MAPK increases the nuclear transcription activity of SRs by phosphorylating the receptor or a coactivator by a feed-forward mechanism; 2) activated MAPK activates other transcription factors (TF) that cooperate with SR on SREs; and 3) mediated transcription of genes without SREs. p-HSP, phospho-heat shock protein.

REFERENCES


