Category :**Sepsis: basic mechanisms**

A144 - ***The systemic inflammatory response induced by lipopolysaccharide administration is more pronounced in women than in men***

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Introduction:

A better understanding of the potential sex-specific differences in the immune response may facilitate personalized treatment approaches for sepsis. We investigated whether sex affects the immune response and the development of endotoxin tolerance in a large cohort of volunteers undergoing repeated experimental human endotoxemia, an established *in vivo* model capturing many hallmarks of both early sepsis and sepsis-induced immunoparalysis.

Methods:

Subjects (54 females and 56 males) were intravenously challenged with 1 ng/kg bacterial lipopolysaccharide (LPS) twice: on day 0 to determine the extent of the inflammatory response and again on day 7 to determine the degree of endotoxin tolerance. Area under the plasma cytokine time-concentration curves (AUCs) were calculated to provide an integral measure of the cytokine response.

Results:

Median [interquartile range] age was 23 [21-25] years for males and 23 [21-24] years for females (p=0.18), whereas BMI was 23.0 [20.8-25.1] and 23.6 [21.9-25.7] kg/m^2, respectively (p=0.12). Compared with males upon the first LPS challenge, females produced significantly higher levels of tumour necrosis factor (TNF, 41% higher AUC), interleukin (IL)-6 (+50%), interferon gamma induced protein (IP)-10 (+47%), and IL-1 receptor antagonist (+112%), but not IL-10 (-4%, Figure 1). Although a tolerant response was observed for all measured cytokines (all p<0.0001 vs. first challenge), no differences in the degree of endotoxin tolerance between the sexes were observed.

Conclusion:

We demonstrate that females mount a more pronounced proinflammatory cytokine response following LPS administration than males, while levels of the anti-inflammatory cytokine IL-10 and the development of endotoxin tolerance were not different between the sexes. These findings indicate sex-specific regulation of the innate immune response. Sex hormone profiles are currently being determined to assess whether these differences have a hormonal origin.

Image :

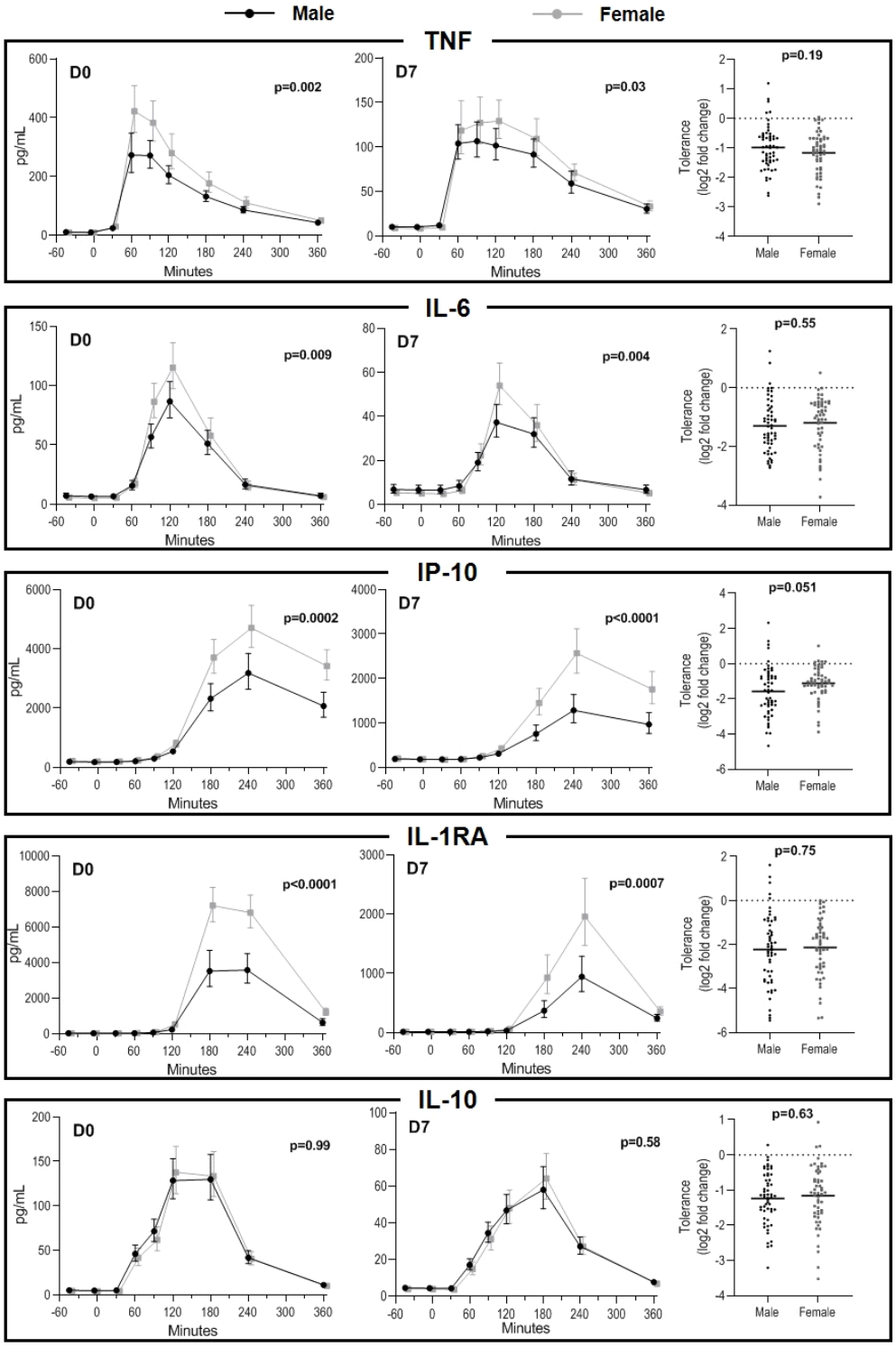

Figure 1. Sex-specific differences in plasma levels of inflammatory mediators following repeated LPS administration on day 0 (D0, left panels) and day 7 (D7, center panels). 1 ng/kg LPS was administered at t=0 on both days. Right panels display the degree of endotoxin tolerance, presented as the log2 fold change in the area under the time-concentrations curves between day 7 and day 0. Data in left and center panels are presented as geometric mean and 95%-confidence intervals, whereas data in the right panels are presented as scatter plots with the horizontal line indicating the mean. P-values were calculated using unpaired student's t-test on log-transformed area under the time-concentrations curve data. TNF = tumour necrosis factor, IL = interleukin, IP = interferon gamma induced protein, RA = receptor antagonist.