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Lipopolysaccharide (LPS) processing by Kupffer cells releases a modified LPS with increased hepatocyte binding and decreased tumor necrosis factor-alpha stimulatory capacity.

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Normal physiological clearance of gut-derived endotoxin lipopolysaccharide [LPS] has been described previously; initially, there is uptake by Kupffer cells (KC), then release of modified LPS, followed by hepatocyte uptake. Previous work in our laboratories indicated that LPS is structurally modified with loss of carbohydrate prior to its release by KC. In this study, we functionally characterize KC modified LPS. KC-modified 125I-LPS was prepared from primary rat KC. Escherichia coli 0127:B8 native 125I-LPS or KC-modified 125I-LPS (40 ng) was incubated for 1 hr with 1 x 10E6 primary hepatocytes. The binding of KC-modified LPS was 4.33-fold higher than native LPS ($P = 0.0024$). Binding analysis studies were conducted to determine the region of KC-modified LPS responsible for enhanced hepatocyte binding. KC-modified Salmonella minnesota LPS was competed with 100-fold excess native or mutant (Ra, Rc, Rd, or Re) strains of LPS or Lipid A with no decrease to hepatocyte binding. S. minnesota-native 125I-LPS was compared with KC-modified 125I-LPS in a study to assess induction of tumor necrosis factor (TNF)-gamma by rat peritoneal macrophages. Native or KC-modified 125I-LPS (100 ng) was presented to 1 x 10E7 peritoneal macrophages for 6 hr. TNF-alpha was measured in supernatants using the WEHI-164 cytotoxicity assay. Native LPS induced 5.7-fold higher TNF-alpha levels than KC-modified LPS ($P < 0.0001$). The above data suggest that structural alterations in KC-modified LPS are accompanied by functional alterations resulting in enhanced hepatocyte binding and decreased TNF-alpha release. The latter result implies that an early step in LPS detoxification occurs in the KC in which LPS is modified to prevent elicitation of biologically active cytokines.