METABOLIC EFFECTS OF ENDOTOXIN

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GENERAL CONSIDERATIONS

Endotoxins, derived from gram-negative organisms, elicit a variety of effects in the host. Notable among these are the immunologic and anti-tumor effects, disseminated intravascular coagulopathies, the release of a large array of leukocyte-derived mediators, metabolic and endocrine alterations, etc. Many of these effects have been discussed extensively elsewhere in this monograph e.g., immunologic, anti-tumor effects, mediators. The aim of this communication is to briefly summarize the metabolic alterations affecting carbohydrate homeostasis following endotoxin administration. We will focus primarily on experimental results obtained in our laboratories, fully recognizing that major contributions by other laboratories have continuously modified our own thinking.

The bacterial origin of endotoxins does not appear to influence their major biologic effects. Furthermore, while marked species differences exist in respect to endotoxin sensitivity, it appears that many of the hormonal and metabolic alterations elicited by endotoxin are quite similar in a variety of animal species that have been investigated. Because of the differences in sensitivity to endotoxin, we feel that in metabolic investigations studying endotoxin effects, it is important to relate the observed alterations to the severity of the insult, as expressed by the degree of lethality within a given time period (e.g. LD10, or LD50 within 24 hrs), rather than indexing the produced effects to the absolute dose administered.

Administration of endotoxin to animals has been employed for some time as a tool to advance our understanding of sepsis and septic shock. At times, the use of endotoxin has been criticized because the changes that take place in endotoxin-treated animals do not always mimic those observed in septic patients. Indeed, one has to be quite careful in extrapolating the results obtained in animals following endotoxin to man in gram-negative sepsis. Several factors must be considered in this connection: first, the species under study may respond to sepsis and endotoxin differently from man (at least in certain respects); second, most endotoxin studies are designed to investigate the shock phase of sepsis and employ large bolus injections. At best, these types of studies can relate to only the severe stages of septic shock. Thus the dose of endotoxin used in comparison to the amount that might be present during sepsis must be considered; third, one must consider the overall state of the endotoxemic animal at the time the
specific measurements are made; fourth, it must be recognized that it is very difficult to administer endotoxin in a manner that simulates its presence during sepsis; and, finally, one must consider that the septic patient is usually studied while given clinical and pharmacologic support, which is designed to improve the clinical outcome but which may complicate the comparison to animal studies. There is little doubt that the clinical manifestations of sepsis are not due exclusively to a response to in vivo released endotoxins; however, it is also evident that many aspects of sepsis can be mimicked by endotoxin administration. This has been demonstrated repeatedly in endotoxic shock. More recently we have found that the metabolic alterations described in hypermetabolic, hyperdynamic sepsis (12) are quite similar to those found following the administration of very low, nonlethal doses of endotoxin in experimental animals (6,13). Most of the sepsis-induced metabolic alterations are also reproduced when endotoxin is delivered over a period of several hours, and even days, by the recently-developed experimental technique of subcutaneously-implanted osmotic mini-pump (24). These new approaches promise more precise assessments of the importance of endotoxins in producing some of the manifestations of sepsis.

DISSOCIATION OF THE HEMODYNAMIC, METABOLIC AND HYPERThERMIC EFFECTS OF ENDOTOXIN

Numerous investigators have described the cardiovascular sequelae of the administration of lethal doses of endotoxin, which include systemic hypotension, decreased cardiac output and increased heart rate. These cardiovascular changes are accompanied by an initial hyperglycemia followed by hypoglycemia (if the administered dose is high), hyperlactacidemia and increased glucose turnover and hepatic gluconeogenesis (26) all of which appear to be dose-dependent. Preterminally, the elevated rate of gluconeogenesis is replaced by a marked decrease in this variable (27). In most species, the administration of lethal doses of endotoxin also evokes hypothermia. In a recent investigation, we attempted to separate the hemodynamic, metabolic and thermal effects of E. coli endotoxin by evaluating changes that take place in chronically-catheterized, conscious rats when administered a wide range of endotoxin doses (13). Very low, nonlethal doses of endotoxin caused alterations in carbohydrate metabolism, (e.g., increased glucose turnover and arterial lactate concentration) but did not produce hemodynamic changes, (i.e., a fall in blood pressure and cardiac output). These metabolic changes could be elicited with a dose of endotoxin that was one hundredth of the amount needed to produce cardiovascular alterations, thus making possible the separation of metabolic effects from hemodynamic alterations. In the same studies, different doses of endotoxin elicited either an increase or a decrease in body temperature: at high doses, hypothermia was the characteristic feature, while at very low, nonlethal doses hyperthermia was present. Thus, the thermal effects could also be separated from both cardiovascular and metabolic responses. These findings are summarized in Figure 1. Although the original study from which these data were reproduced included six doses of endotoxin, for the sake of an easy overview this figure represents results following only two: the higher one represents an LD_{50} (in 24 hrs) whereas the lower is three orders of magnitude less than that required to produce an LD_{50} effect. With the LD_{50} dose the metabolic responses seemed to parallel hemodynamic changes. However, the lower dose, which failed to alter the hemodynamic variables, still induced metabolic effects as evidenced by alterations in glucose turnover and arterial lactate concentration. Also, while the high dose decreased core body temperature, the lower one produced a fever response in these animals.

A closer perusal of the results indicates that the metabolic effects observed following the very low dose of endotoxin were delayed when compared