

## ENDOTOXINS AND ENDOCRINE SYSTEM

L. Bertók

Frederic Joliot-Curie" National Research institute for Radiobiology and  
Radiohygiene, Budapest, H-1775 P.O.B. 101, Hungary

Received November 21, 1997  
Accepted February 13, 1998

There is good evidence for the interaction of neuroendocrine and immune systems. Endotoxin (LPS)-induced mediators (e.g., cytokines, prostaglandins etc) set on endocrine organs (e.g., the hypothalamo-pituitary-adrenal axis: thyroid glands etc). Endotoxin-treated, intestinal ischemic, or irradiated rats show decreased  $T_4$  levels of blood. These animals cannot respond to TSH because the TSH-receptors of follicular membranes are disturbed by LPS in the thyroid glands. Radiodetoxified endotoxin is an effective immunostimulator and does not disturb the follicular membrane of thyroid gland. Thus, the  $T_j$  production remains normal. The bile acids—as the end-product of cholesterol metabolism—play an important role in the physiological defense of macroorganisms against endotoxin and other lipid-like agents (Physico-chemical defense) and in the regulation of endocrine system, including the reproduction. © Elsevier Science Inc. 1998

Endotoxin is a biologically highly active macromolecule. Its membrane damaging, capillary permeability increasing, pyrogenic and shock-provoking effects are well known. The membrane damaging effect is probably attributable to the fact that the endotoxin macromolecule (lipopolysaccharide: LPS) binds to the lipid bilayer of the membrane and causes its perturbation. The cell wall of gram-negative bacteria (*Escherichia coli*, *Proteus vulgaris*, etc.) contain LPS and is constantly present in the intestinal flora of humans and animals. Under physiological conditions LPS is cleaved to non-toxic fragments under the detergent action of bile. Endotoxin can only be absorbed (translocated) from the gut and cause enteroendotoxaemia if no bile is present for some reason (1,2).

It seems that in LPS shock the hormonal signaling might be disturbed. It was demonstrated that in LPS shock the plasma adrenocorticotropin (ACTH) increased, whereas TSH, prolactin, triiodothyronine ( $T_3$ ) and thyroxine ( $T_4$ ) are decreased. It is possible, that the reduction of TSH,  $T_3$ , and of  $T_4$  is attributable to the damage of the specific hormone receptors in the membrane of corresponding cells (3,4).

The response of the organism to disturbances of its homeostasis caused by LPS is referred to as an acute-phase response. The neuroendocrine and immune systems are involved in functionally relevant cross-talk, and serve to restore the equilibrium of the *milieu interieur* in response to these disturbances. The activation of the hypothalamic-pituitary-adrenal (HPA) axis plays an important role in this process (5,6).

However, the mechanisms through which LPS stimulates the HPA axis and the exact site of its action within the HPA axis are unclear. Hypothalamic lesions and pharmacological blockade of corticotropin-releasing factor (CRF) release suggested that the hypothalamus mediates stimulation of the HPA axis by LPS. LPS could stimulate corticosterone secretion even after removal of the medial hypothalamus. Recently, interleukin-1 (IL-1) and IL-6 produced mainly by activated macrophages and monocytes during stimulation with LPS have been implicated in the activation of the HPA axis (6).

Evidence has been accumulated that there is an interaction between the neuroendocrine and the immune system, and they are able to regulate each others function (7). LPS has been often used to study how the stimulation of the immune system activates the HPA axis (5).

Since TSH receptors are membrane receptors it seemed worthwhile to investigate whether LPS that causes a general membrane destruction would produce such changes in the membrane of thyroid cells. TSH treatment in the perinatal period, i.e. during the membrane perturbation caused by LPS, would restore or influence in any way the responsiveness of the damaged membrane (3).

The pathogenesis of certain experimental shock conditions may involve translocation of bacterial LPS from the gut. It has been investigated how the basal T<sub>4</sub> serum level changed in response to exogenous TSH treatment. For these the following models were selected: the LPS-shock, the superior mesenteric artery occlusion (SMAO) tourniquet shock and radiation disease.

Low serum T<sub>3</sub> and T<sub>4</sub> levels are common after infectious illness and LPS-induced fever of experimental rabbits. It seems probable that during infectious diseases, early suppression of TSH-release and subsequent decrease of T<sub>4</sub> secretion occurs. At the same time it is well known that experimental LPS shock diminishes plasma TSH levels. In earlier examinations it was demonstrated that i.v. LPS decreases serum T<sub>4</sub> level in rats and inhibits the T<sub>4</sub> response to exogenous TSH (4). It has also been stated that subtoxic amount of LPS given intraperitoneally (i.p.) to newborn rats decreases adult T<sub>4</sub> level and moderated the response to exogenous TSH (3). All these data indicate that the membrane damaging effect of bacterial LPS entering the circulation may play a role in the change of the function of the thyroid gland. Because pathogenesis of certain experimental shock conditions may involve absorption of bacterial endotoxins, it seemed worthy to investigate how the basal level of T<sub>4</sub> of the serum changed in response of thyroid gland to exogenous TSH treatment (8).

In the superior mesenteric artery occlusion (SMAO) induced shock (intestinal ischemia) the T<sub>4</sub> level significantly decreased. TSH treatment did not influence the serum T<sub>4</sub> level compared to the controls (9). In the tourniquet shock the changes of T<sub>4</sub> level were similar but more moderate. Due to ischemia biogen amines are being formed in large amount in the tissues after the release of the ligature and they enter the circulation producing and enteroendotoxemic shock, too (10). In our earlier experiments—using lead acetate induced LPS hypersensitivity (11)—it was demonstrated that the intestinal syndrome of radiation disease is an enteroendotoxemia (12). The irradiated animals on Day 7 of the irradiation showed even more severe clinical symptoms of radiation disease. The high dose whole-body irradiation significantly decreased the function of thyroid gland of rat and even inhibited the T<sub>4</sub> response to exogenous TSH. We suppose that this effect is induced by the LPS, which is translocated from the intestinal tract (13). The general membrane damaging effect of LPS and their interactions with other hormone receptors in our assumption appears to be an acceptable idea.

These observations call the attention to the fact that differently induced experimental shock models (e.g., LPS shock, intestinal ischemic shock, tourniquet shock, and so-called intestinal syndrome of the acute radiation disease) can produce similar changes in the function of the thyroid gland (8,9,14).

It has long been known that the toxic effects of LPS under experimental conditions can be induced only when administered parentally. However, in naturally occurring enteroendotoxemic disease (e.g. septic and intestinal ischemic shocks) LPS absorbs from the intestinal tract to the blood circulation and can elicit pathological processes. This is an important distinction between natural and experimental LPS shock. When the common

bile duct of rats was chronically cannulated a significant amount of perorally administered LPS translocated into the blood. This LPS shock could be prevented by bile acids (2). The physiological surfactants, the bile acids, are important factors in the defense of microorganisms against endotoxins (physico-chemical defense) (1). The production and passage of bile acids depend on liver function and on cholecystokinin (CCK) synthesis by the small intestine wall. If the bile (bile acid) content of the intestinal canal decreases endotoxin can translocate to the body and elicits toxic symptoms. So, most important parts of defense against endotoxins in natural conditions are the CCK and bile acids. The consequence of liver damage (place of bile acid synthesis) or damage of the small intestine (place of CCK synthesis) is the absorption of endotoxins (15).

The bile acids are the product of cholesterol metabolism. Cholesterol is also the precursor for all steroid hormones. So if the cholesterol-bile acids transformation or entero-hepatic circulation is insufficient the metabolism of all steroid hormones could be disturbed. In bile deficiency endotoxin can translocate from the intestinal tract to the blood and can disturb liver function (e.g., cholesterol metabolism etc.) and consequently steroid hormone production. So, bile acids could play an important role in function of the endocrine organs (14,15).

It has long been known that bacterial LPS may induce fetal death, fetal absorption, abortion, and malformations in experimental animals, particularly in LPS sensitive species (golden hamster, swine), but also in human beings (16).

The majority of earlier investigations focused on the effect of LPS placental changes in the third trimester of pregnancy. Only a few reports have been concerned with the effect and consequences of endotoxemia during placentation. It is also known that numerous effects of LPS cannot be prevented or warded off by small doses of LPS administered parentally. This phenomenon is called LPS-tolerance. For this purpose a bacterial LPS preparation, detoxified by <sup>60</sup>Co-gamma (RD-LPS: 17, IS) has been used in our laboratory. This preparation has also been applied in our experiment (19,20). Examinations with RD-LPS—which has practically no membrane damaging effect—we produced new data in support of our view (21).

During the LPS shock in adult rats' the plasma T<sub>4</sub> level decreased markedly and was not compensated by administration of exogenous TSH. However, the RD-LPS treatment did not inhibit the response to exogenous TSH and decreased serum T<sub>4</sub> level to a lesser extent than unirradiated LPS. Our results proved that RD-LPS lost its membrane-perturbing effect. It is attractive to consider that RD-LPS might be similar to the parent (toxic) LPS in some respects. However, in contrast to parent LPS, the RD-LPS is unable to initiate the processes leading to irreversible membrane damage. Concerning the general membrane damaging effect of LPS and its interactions with other hormone receptors we supposed that the membranes of follicular cells could have changed and/or the number of TSH receptors, have decreased.

#### REFERENCES

1. Bertók L. Physico-chemical defense of vertebrate [orfia.iii.rm](#): The role of bile acids in defense against bacterial endotoxins. *Proc Biol Med* 21:70-76. 1977.
2. Kocsis L. Bertók L. Vártszács V. Effect of bile acids on the intestinal absorption of endotoxin in rats. *J Bact* 10(1):220-223. 1969.
3. Nagy S. Csaba G. Benók L. Influence of neonatal endotoxin treatment and hormonal imprinting on thyrotropin induced thyroxin (T<sub>4</sub>) production of adult rats. *Acta Physiol Hung* 62:151-153. 1983.
4. Nagy S. Csaba G. Benók L. Effect of thyrotropin (TSH) treatment on the responsiveness of the thyroid gland during endotoxin shock in adult rats. *Acta Physiol Hung* 62:187-190. 1983.
5. Elenkov U. Kiss J. Stark E. Bertók L. CRF-dependent and CRF independent mechanisms involved in hypothalamic-adrenal system activation by bacterial endotoxin. *Acta Physiol Hung* 79:355-363. 1992.
6. Elenkov I J. Kovács K. Kiss J. Bertók L. Vizi ES. Lipopoly saccharide is able to bypass conicotrophin-

- releasing factor in affecting plasma ACTH and corticosterone levels: Evidence from rats with lesions of the paraventricular nucleus. *J Endocrinol* 133:231-236. 1992.
7. Berczi I. (ed). *Pituitary Function and Immunity*. CRC Press. Boca Raton, FL 1986.
  8. Nagy S, Bertók L. Influence of experimentally induced endotoxemias on the thyroid function of rat. *Acta Physiol Hung* 76:137-144. 1991.
  9. Nagy S, Bertók L. Effect of experimental shock conditions on the serum T<sub>4</sub> level of rats and response of their thyroid gland to exogenous TSH. *Z exp Chir Transplant* 20:113-116, 1987.
  10. Orbán I, Bertók L, Regős J, Gazsó L. Die Rolle der bakteriellen Endotoxine beim Tourniquet Schock der Ratte. *Acta Chir Acad Sci. Hung* 19:399-404. 1978.
  11. Selye H, Tuchweber B, Bertók L. Effect of lead acetate on the susceptibility of rats to bacterial endotoxins. *J Baa* 91:834-890. 1966.
  12. Bertók L, Kocsár L. Die Rolle des Endotoxins beim intestinalen Syndrom der Strahlenkrankheit. *Wiss. Z. K. Marx-Univ. Leipzig. (Math.-Naturwiss.)*. 23:65-66. 1974.
  13. Bertók L, Nagy S. Effect of irradiation on serum T<sub>4</sub> level and response of thyroid gland to exogenous TSH, in rats. *J Radiat Res* 27:225-229, 1986.
  14. Bertók L. Bacterial endotoxins and nonspecific resistance. In: *Traumatic Injury: Infection and Other Immunologic Sequelae*. Ninnemann, J.L. (ed). University Park Press. Baltimore, MD pp. 119-143, 1983.
  15. Bertók L. Role of endotoxins and bile acids in the pathogenesis of septic circulatory shock. *Acta Chirurg Hung*. 36:33-36, 1997.
  16. Csordás T, Bertók L, Csapó Zs. Experiments on prevention of the endotoxin-abortion effect by radiodetoxified endotoxin pretreatment in rats. *Gynecol. Obstet Invest* 9:57-64. 1978.
  17. Bertók L. Radio-detoxified endotoxin as a potent stimulator of nonspecific resistance. *Persp Biol Med* 24:61-66. 1980.
  18. Bertók L. Stimulation of nonspecific resistance by radio-detoxified endotoxin. In: *Endotoxin*, Friedman H., Klein TV, Nakano M, Nowomy A. (eds). Plenum Publishing, pp. 677-680. 1990.
  19. Szócs Gy, Csordás T, Benók L. Study of the endotoxin sensitivity of pregnant rats and their fetuses. *Acta Chirurg Hung* 31:263-269. 1990.
  20. Szócs Gy, Csordás T, Benók L. Effect of bacterial endotoxin on placentation of rats. *Acta Chirurg Hung* 31:169-174. 1990.
  21. Bertók L, Nagy S. The effect of endotoxin and radio-detoxified endotoxin on the serum T<sub>4</sub> level of rats and response of their thyroid gland to exogenous TSH. *Immunopharmacology* 8:143-146, 1984.