

Anorexia: the toll for lipopolysaccharide recognition

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THE REVIEWS OF Hart (13) and Kent et al. (20) have drawn attention to the so-called sickness syndrome, a suite of autonomic and behavioral manifestations (sickness symptoms or responses) of systemic inflammation. The syndrome unites sickness responses (e.g., fever, hypothermia, hyperalgesia and/or allodynia, hypoalgesia, sleep, and anorexia) that have different latencies and durations and follow one another as the disease progresses (32, 33). Although sickness responses, when unchecked, can have pathological consequences, they are generally believed to be adaptive (13, 20, 33). The sickness syndrome is often induced in the laboratory by injecting animals with bacterial LPS. Recent articles published by the *American Journal of Physiology-Regulatory, Integrative and Comparative Physiology* are dedicated to mechanisms of several sickness symptoms occurring in response to LPS: fever (3, 8, 9, 12, 16–19, 23, 26, 35), activation of the hypothalamo-pituitary-adrenal axis (10, 19), and anorexia (24, 39). The article by von Meyenburg et al. (39) in the current issue examines whether two proteins involved in LPS signaling, the glycoprotein CD14 and Toll-like receptor 4 (TLR4), are required for LPS-induced anorexia. These two proteins—along with myeloid differentiation protein-2 and LPS-binding protein—are considered the key molecules for LPS recognition. Cellular TLR4 recognizes LPS and responds to it only after LPS interacts with CD14 (1, 27, 31; for additional references, see Ref. 39). By studying food consumption in genetically modified mice, von Meyenburg et al. (39) showed that the anorectic response to LPS is reduced in both CD14 knockouts and TLR4-deficient mutants, thus indicating that CD14 and TLR4 are required for the development of LPS-induced anorexia.

This observation is important because anorexia was viewed for many years as the “black sheep” among the responses to LPS. Early findings by J. H. Brobeck and others showing that body temperature affects food consumption (e.g., Ref. 2) led to the belief that infection-associated or LPS-induced anorexia is not an independent response but that it occurs secondarily to fever, simply reflecting the dependence of food intake on body temperature. This belief was later disproved by showing that LPS-induced anorexia is unrelated to body temperature (22, 25). There was also reason to suspect that LPS causes anorexia via an atypical signaling pathway specific for this response. Administration of LPS results in tolerance, a state in which responses to subsequently administered LPS are decreased (for review, see Refs. 4, 5). This is true in regards to the febrile, hypotensive, antidiuretic, hyperglycemic, leukopenic, and many other responses. As an exception to this rule, the anorectic response was found to occur in tolerant rats in a study by O'Reilly et al. (28), although the same animals developed no febrile response. However, this unusual result was not

confirmed by subsequent studies (7, 21) and was thought to reflect a methodological peculiarity (21).

The article of von Meyenburg et al. (39) also reports an interesting observation that the absence of another Toll-like receptor, TLR2, does not affect LPS anorexia. This observation is important, because, until recently, TLR2 was thought by some to recognize LPS (37) and mediate LPS-induced sickness symptoms such as fever (6). However, Hirschfeld et al. (14) demonstrated that it is not LPS per se but rather a highly bioactive lipopeptide contaminant of LPS preparations (“endotoxin protein”) that signals through TLR2. The same receptor, TLR2, plays a major role in recognition of cell wall constituents of gram-positive bacteria, e.g., muramyl dipeptide (36, 38). In agreement with such a role, von Meyenburg et al. (39) showed that muramyl dipeptide-induced anorexia is attenuated in TLR2-knockout mice.

In addition to the molecules mentioned above, LPS recognition may involve other receptors, most notably CD11/CD18 β_2 -integrin (30) and cell-surface proteins known as scavenger receptors (29). Gioannini et al. (11) list several more examples of proteins that may participate in cellular activation by LPS depending on specific structural features of particular LPS species, the host cell types examined, and the response studied. It is possible, therefore, that some of these molecules can also contribute to triggering the sickness syndrome, and von Meyenburg et al. (39) acknowledge such a possibility. This possibility seems likely because the same dose of LPS can cause different responses in the same species depending on the experimental conditions, e.g., rats respond to LPS with fever at a neutral ambient temperature but develop hypothermia (at least transient) at a subneutral temperature (17, 34). Such duality of LPS action has been speculated (15) to reflect different distribution of the blood in the body at different ambient temperatures and, consequently, different distribution of LPS and its recognition by different cells possibly via different receptors. A better understanding of the recognition systems and mechanisms of their coupling with different sickness responses may pave the road for development of new therapeutic approaches. The article by von Meyenburg et al. (39) is an important pavestone on this road, or should I say toll road?

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