Waste not, weak not?

When we catch a cold or the flu, most of us experience a sensation of “tiredness” or “weakness” that makes it difficult to go about our daily tasks. Weakness is a common symptom of infectious processes. A Medline search that cross-references “infection” and “weakness” yields over 1,900 references. This extensive literature documents muscular weakness in processes that range from food poisoning (2) to malaria (4) to intrauterine fungal infection (11). Weakness is especially common in individuals with blood-borne infections, termed sepsis, and can affect the muscles of respiration (7). This poses serious consequences for health. Respiratory muscle weakness predisposes septic individuals to respiratory insufficiency and dependence on a mechanical ventilator, increasing the risk of complications and prolonging hospitalization.

The mechanisms by which infections cause muscle weakness remain poorly understood. Apart from conditions that affect the nervous system or neuromuscular transmission, muscle weakness is generally attributed to loss of muscle mass (6). Inflammatory mediators can stimulate muscle catabolism by accelerating protein degradation (1). Therefore, the general model is that infection stimulates inflammation that leads to muscle wasting and thereby weakness (see Fig. 1).

But this model does not always apply. Force decrements are not universally explained by muscle atrophy (3, 5, 8, 10). In the early stages of infection, for example, weakness may precede overt loss of protein such that existing muscle generates less-than-normal force (2, 4, 11). This suggests that infection or the associated inflammatory response can cause contractile dysfunction, leading to weakness without wasting.

In this issue of the Journal of Applied Physiology, Supinski and Callahan (9) elegantly demonstrate muscle weakness without wasting in an experimental model of sepsis. The investigators injected mice with endotoxin, a lipopolysaccharide derived from bacterial cell walls, and documented profound loss of contractile function in the diaphragm. This weakness was not associated with diaphragm atrophy. Neither muscle weight nor protein content was changed. Rather, weakness was wholly attributable to a decrement in force per cross-sectional area, which fell by one-half, and was linked to a rise in caspase 3 activity. Pharmacologic caspase blockade completely abolished the muscle weakness caused by endotoxin, establishing a causal relationship.

These observations are the first to demonstrate that caspase activity contributes to the weakness caused by infection. Two previous reports have associated caspase activity with myocyte apoptosis (12, 13), suggesting a role in muscle atrophy, but caspase-induced contractile dysfunction has never been proposed in skeletal muscle. This discovery triggers a flurry of subsequent questions. For example, what causes caspase activation in muscle? What is the molecular target of caspase action that causes contractile dysfunction? Do caspases mediate weakness in other conditions that diminish force per cross-sectional area, e.g., sarcopenia of aging (3), prolonged bed rest (10), cardiac cachexia (5), and cytokine stimulation (8)?

Supinski and Callahan (9) have also identified a novel target for drug development. There is no pharmacologic intervention for the diaphragm weakness that develops during sepsis, no drug to treat the ventilatory failure that commonly occurs in these individuals. If caspase inhibitors protect diaphragm function in septic humans, such drugs would be of enormous clinical benefit in the management of critically ill patients. Clearly, the current report by Supinski and Callahan will be of interest to researchers and clinicians alike.

REFERENCES


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