Calpain and caspase-3 are required for sepsis-induced diaphragmatic weakness

Scott K. Powers
Department of Applied Physiology and Kinesiology, University of Florida, Gainesville, Florida

It is well established that many critically ill patients exhibit severe respiratory muscle weakness. This weakness could be due to many interacting factors, including malnutrition, cancer-mediated cachexia, mechanical ventilation-induced diaphragmatic dysfunction, and sepsis. In regard to muscle wasting in critically ill patients, sepsis is of particular importance, because systemic infections can promote dramatic reductions in diaphragmatic force-generating capacity in as few as 24 h (6). This sepsis-induced skeletal muscle weakness is clinically important for many reasons. For example, respiratory muscle weakness is likely a frequent contributor to the inability to wean patients from mechanical ventilation (1). Furthermore, significant loss of strength in leg muscles is a common contributor to falls in weak patients (5).

Given the rapid and dramatic negative impact that sepsis has on skeletal muscle function, it is important to understand the cellular mechanisms responsible for sepsis-induced muscle weakness. Using a clinically relevant model of sepsis (i.e., cecal ligation perforation model), Supinski and colleagues (8) demonstrate that both calpain I and caspase-3 are activated in the diaphragm during sepsis, and that each of these proteases contributes to sepsis-induced muscle weakness. Importantly, this work also demonstrates that the sepsis-induced activation of calpain I and caspase-3 in the diaphragm occurs in parallel rather than due to an interaction between calpain and caspase-3. This is significant because, during both disuse muscle atrophy and ischemia-induced proteolysis, it is postulated that cross talk between calpain and caspase-3 plays an important role in regulating the activity of each protease (3, 4). Specifically, active calpain can participate in the activation of caspase-3 via a mitochondrial-mediated pathway (3). Furthermore, active caspase-3 is capable of degrading calpastatin, which is the only known endogenous inhibitor of calpain. Hence, activation of calpain could activate caspase-3 and vice versa (3).

The present and previous findings of Supinski et al. support the notion that muscle proteolysis occurs via a two-step process (7). Specifically, in the first step, myofilaments are released via the proteolytic action of calpain and/or caspase-3 (2). In the second step, the released myofilaments are then degraded by the proteasome system. Hence, the work of Supinski and colleagues indicates that the activation of calpain and caspase-3 is the rate-limiting step in sepsis-induced diaphragmatic weakness.

In summary, I applaud Supinski and colleague’s contribution to our knowledge regarding the role that calpain and caspase-3 play in sepsis-induced respiratory muscle weakness. Their findings are important and pave the way for further studies. In this regard, additional work should determine whether calpain and caspase-3 work independently or cooperatively in their degradation of the contractile protein lattice during sepsis. Also, future studies on this topic will likely be directed toward understanding the cell signaling links between sepsis and the activation of calpain and caspase-3 in muscle fibers. A detailed understanding of these signaling mechanisms could lead to therapeutic interventions that are capable of preventing or retarding sepsis-induced muscle wasting and contractile dysfunction.

REFERENCES