

relating to the role of disturbed Ca^{2+} regulation in sepsis. The main emphasis will be on the skeletal muscle disorder due to Ca^{2+} imbalance during pathophysiological conditions and importance of some cytokines in mediating the tissue injury.

1. Pathophysiology of cellular calcium regulation

In general, living cells maintain the cytosolic Ca^{2+} concentration at submicromolar levels (≈ 100 nM) in comparison to the millimolar range in the extracellular compartment. Thus a steep gradient of Ca^{2+} concentration exist both across the plasma membrane and the endoplasmic reticulum (ER) (10, 12).

At least four processes control Ca^{2+} exchange at the plasma membrane - a passive Ca^{2+} leak dependent/independent upon membrane potential, specific Ca^{2+} pumps and Ca^{2+} -Na exchangers. Events at the plasma membrane, ER, and inner mitochondrial membrane are all involved in regulating the intracellular Ca^{2+} concentrations $[\text{Ca}^{2+}]_i$ in concert. Besides these above mechanisms of calcium flux, receptor and voltage operated calcium channels have already been reported. These processes include cyclic AMP, inositol triphosphate and diacylglycerol. However, importance of G proteins in all these processes can not be neglected. Transient elevations of $[\text{Ca}^{2+}]_i$ occur with stimulation of the tissue and lead to physiological cellular response. Impairment or perturbation of the mechanisms which regulate cytosolic Ca^{2+} level can result in sustained elevation of cytosolic Ca^{2+} to above physiological levels. For example a

pathophysiological or pathological increase in Ca^{2+} influx from extracellular to cytosolic compartment or a decrease in Ca^{2+} movement from cytosol to sarcoplasmic reticulum (SR) could contribute to a sustained elevation in cytosolic $[\text{Ca}^{2+}]_i$.

2. Intracellular calcium during endotoxic/septic injury in excitable and non-excitable tissues

A. In muscles: Intracellular Ca^{2+} in skeletal muscle is important in the regulation of both contractile and metabolic responses which are vital under physiological conditions not only for the integrity of skeletal muscle itself but also for the organism as well. A disturbance in the intracellular regulation of Ca^{2+} leading to altered cytosolic $[\text{Ca}^{2+}]_i$ and/or altered movements of Ca^{2+} across the plasma membrane or the organelle membrane could evidently interfere with the above mentioned processes.

Intracellular Ca^{2+} overload has been implicated in ischemia and considered to be a lethal event after cell injury of various etiologies (13). Previous studies (14,15) were undertaken to determine whether cellular Ca^{2+} regulation is altered in bacteremic rat skeletal muscle, where $^{45}\text{Ca}^{2+}$ uptake was measured in slow-twitch soleus muscles after *Escherichia coli* injection. Bacteremia had very little effect on steady-state exchangeable Ca^{2+} but it significantly reduced the time required to reach half-maximal uptake compared with controls (14,15). These changes were checked by diltiazem, a Ca^{2+} -channel blocker in bacteremic skeletal muscle. Further, depolarization of soleus muscles with high K^+ (60 μM) transiently increased Ca^{2+} uptake both in control and bacteremic rat

muscles, but bacteremic muscles showed a greater increase. These studies indicate that the altered Ca^{2+} regulation may be due to stimulation of Ca^{2+} messenger systems, sarcolemmal Ca^{2+} channels or release of Ca^{2+} from SR in response to bacteremia. Further, alteration in intracellular Ca^{2+} regulation was also studied (16) using intraabdominal abscess (IAA) model of sepsis instead of short term bacteremic model as used by previous workers (14). This IAA model, is a chronic model where predetermined types and numbers of gram-negative bacteria are implanted into the rat abdominal cavity. The doses of bacteria chosen were such that it could produce 20–30% mortality during the period of sepsis and injury produced in the skeletal muscle was mild rather than highly lethal. In this study (16), an elevation of Ca^{2+} flux was noted in soleus muscle in comparison to non-septic muscle during 2–3 days of implantation whereas on 4th day the increased Ca^{2+} flux was subsided and comparable to non-septic values. Not only Ca^{2+} flux, but the rate of uptake was also different between non-septic and septic group. Parallely, net protein catabolic response was significantly different in septic muscles in comparison to non-septic model (16).

The increased skeletal muscle Ca^{2+} -flux suggests an increased rate of Ca^{2+} transport into SR (18) associated with increased SR release of Ca^{2+} and thus increased availability of Ca^{2+} for the activation of Ca^{2+} -dependent cellular processes of muscle including proteolysis via Ca^{2+} -dependent proteases. Both these parameters, proteolysis and Ca^{2+} -dependent proteases, were significantly increased in septic muscles (16, 17) as a functional change

during intraabdominal sepsis.

Following short term septic model of cecal ligation and puncture, Song et al. (19) studied the role of $[\text{Ca}^{2+}]_i$ in the pathophysiology of sepsis. Using ^{19}F NMR spectroscopy and the calcium indicator they showed in the intact perfused rat thoracic aorta, that $[\text{Ca}^{2+}]_i$ in aortic smooth muscle is increased more than 2-fold during sepsis. Further, dantrolene, a drug that prevents mobilization of Ca^{2+} from intracellular stores, reduced the elevated $[\text{Ca}^{2+}]_i$ in sepsis to control values when added *in vitro* or when given *in vivo* to the animal. The same group (20) also studied whether $[\text{Ca}^{2+}]_i$ is responsible for the major metabolic changes of sepsis and whether dantrolene could affect the metabolic abnormalities in plasma and epitrochlearis muscles of septic rats. Their observation (20) suggested that dantrolene could prevent the major metabolic changes in septic muscles. They have further shown that the same drug could improve the survivability of endotoxic mouse.

Thus all these results (14–20) together clearly indicate that both in the long term intraabdominal septic- and in short term cecal ligation and puncture model an increase in $[\text{Ca}^{2+}]_i$ is an early event in sepsis and that this elevated level of Ca^{2+} may play a role or contribute to the cell injury.

B. In non-excitabile tissues: Endotoxic shock was also induced in rats to study alterations in cellular Ca^{2+} regulation in the liver (21). Liver slices were used to measure Ca^{2+} flux from the intracellular Ca^{2+} pool. Using ^{45}Ca uptake method, ER calcium uptake

measured in control and endotoxic (Salmonella enteritidis 15 mg/kg), rat liver. The effect of *in vitro* administration (250 µg/ml) of endotoxin was also taken for ⁴⁵Ca efflux and uptake of liver slices. Results showed (21) that intracellular Ca²⁺ pool size and norepinephrine regulation of cellular calcium were adversely affected in endotoxic shock. It was suggested that the increased sequestration of Ca²⁺ in the intracellular pool in endotoxic rat liver cells could be due to an influx of extracellular Ca²⁺ and may predispose these cells to Ca²⁺ overload. Thus calcium regulation appeared to be altered in the livers of endotoxic and septic rats (22–26). Very recently studies were undertaken (27) to check whether such intracellular Ca²⁺ related changes could induce the immune (T-lymphocytes) of spleen during sepsis and whether these alterations are related to immune cell dysfunction. Further observations suggest that ConA-mediated proliferation of T-cells in spleen cause a decrease in cellular Ca²⁺ signalling and a decrease in host's resistance against sepsis (27).

3. Effect of Ca²⁺-blocker during sepsis

The chemically relevant Ca²⁺-antagonists i.e. verapamil, nifedipine, diltiazem are known to inhibit intracellular Ca²⁺ dependent functions by interfering with transmembrane Ca²⁺ movement (28, 29). In cardiac and smooth muscle, these compounds exhibit a use-dependent and voltage-dependent blockade of Ca²⁺ inward-current (28, 29). As these Ca²⁺ antagonists are responsible for attenuation of agonists – a receptor operated Ca²⁺ channel activity, they also have importance in the therapeutic efficacy in certain cardiac diseases.

Ca²⁺ channel blockers are known to prevent agonist or receptor operated calcium channel activity in tissues, like liver (30) and smooth muscle (31), they may have a role as therapeutic agents against hyperfunction of any one of the above stated activities. A calcium channel hyperfunction could contribute to altered cellular Ca²⁺ homeostasis including Ca²⁺ overload. A great deal of studies were undertaken with diltiazem, in endotoxic, bacteremic and septic rat muscles and liver (14,16,24). All these observations pointed out that treatment of animals with diltiazem attenuated shock related disturbances in intracellular Ca²⁺ homeostasis. Restoration of Ca²⁺ homeostasis would lead to the restoration of Ca²⁺ dependent cellular action. This drug when administered *in vivo* in rats or *in vitro* to the perfusion medium could decrease elevated [Ca²⁺] level due to sepsis (20). Hotchkiss and Karl (20) have also shown that dantrolene caused 2-fold improvement in survival in endotoxic mice.

A diversity of toxic insults including several cytotoxic drugs, ischemia, tissue injury, sepsis due to bacteremia or endotoxin are known to alter tissue calcium content significantly. These agents may exert their effects initially by disrupting intracellular calcium homeostasis. The elevated free calcium in cytosol that are beyond physiological level, either in duration or in magnitude may excessively activate a variety of calcium dependent enzymes as proteases, phospholipases, endonucleases etc. found at multiple locations within cells. Calcium responsive degradative enzymes activated in an uncontrolled manner may damage plasma membrane in turn and cause further injury, thus upsetting the calcium homeostasis.

A list of diseases associated with an elevated Ca^{2+} level due to injury is given below (Table I). Duncan (40) also suggested that various muscle diseases and examples of experimentally-induced muscle damage

TABLE I : Some conditions increasing Ca^{2+} level.

Type	Reference
Muscular dystrophy	32-34,36
Ischemic injury	13
Cell injury and death	39
Septic injury	16,17,20,24 35,37,38

occur due to elevated level of calcium in the cytosol. Treatment with caffeine or calcium ionophore (A23187) causes increase in proteolytic activity as a result of rise in intracellular Ca^{2+} concentration. This cation might trigger protease activity either directly or indirectly or promote the release of lysosomal enzymes. A detailed discussion on the mechanism of muscle damage during dystrophy has also been discussed (40).

4. Cytokines and immunomodulators in septic injury

Tissue injury/infection produces alterations in host metabolism and homeostasis. A large number of host proteins called cytokines play an integral role in mediating the host response to tissue injury and infection. Of these proteins tumor necrosis factor (TNF) and interleukins (IL) have received much attention for their pathophysiological role in infection and injury. Tissue injury, associated with sepsis, may however participate in the liberation of TNF, IL-1 and IL-6, triggering a series of reaction involving multiple organs, and culminating

in the sepsis syndrome. Endotoxin (LPS), bacterial cell wall product also induces septic shock by activating mononuclear phagocytes to release TNF and interleukins. In this regard, excessive release of TNF/ILs appears to play a pivotal role in mediating host response to gram-negative infection. In the present review, the involvement of cytokines in mediating sepsis is discussed briefly.

Tumor necrosis factor (TNF) : It has long been recognised that the consequences of sepsis are caused by endotoxin which mediates its toxic effect through the stimulation of macrophages. It is reported (41) that endotoxin-resistant mice did not produce TNF in response to septic insult. Injection of high concentrations of TNF in rats produced the symptoms of septic injury (42, 43). Passive immunization with both polyclonal and monoclonal antibodies directed against TNF protected against the injurious effects of endotoxin infusion in murine and primate models of septic shock (44, 45). All these evidences indicate the role of TNF in the pathophysiology of septic shock. A great deal of studies related to TNF and sepsis have been reported by several workers (46, 47).

Interleukins (IL) : IL-1 is a protein or family of proteins (48, 49) which appear to play a major role in the acute phase response, which includes fever, and alteration of hepatic function. Baracos and associates (50) reported increased muscle proteolysis *in vitro* when tissues were incubated with a monocyte supernatant containing IL-1. They further proposed that IL-1 induced elevated concentrations of prostaglandin (PGE_2) and that this was responsible for the increased proteolysis.

However, Moldawer et al. (51) investigating the effect of recombinant-derived human and murine IL-1 on skeletal muscle protein synthesis and breakdown *in vitro* and *in vivo* found that IL-1 had no effect on protein balance even though production of PGE₂ was increased. IL-1 when acts synergistically with TNF produces tissue damage and death in experimental model (52).

The experimental results of Baracos et al. (53) relating the effect of Ca²⁺ and interleukin-1 in muscle protein degradation provides evidence that the mobilization of Ca²⁺ stores in the SR is an early event mediating the action of IL-1 on skeletal muscle. This step appears to stimulate PGE₂ production, which in turn activates protein degradation. Intracellular levels of Ca²⁺ may be a common mediator of IL-1 action on different cell types, since many of the actions of IL-1 are mimicked by the divalent cation ionophore A23187 (40). Further studies are required to establish the effect of IL-1 on the intracellular [Ca²⁺]_i in tissues and whether calcium-blockers inhibit IL-1 action on various cell types.

Interplay between [Ca²⁺]_i and other factors are depicted in the form of a diagram (Fig. 1). It can be seen from the diagram that septic injury is usually associated with gram -ve bacteria and endotoxin (lipopolysaccharide [LPS]), the breakdown product of their cell wall. LPS is already known as a potent activator of immune and endocrine systems (54, 55, 56). It can further be seen that activated monocytes and macrophages and to some extent neutrophils mediate release of cytokines i.e., interleukin -1 and -6 and transforming growth factor. Prostacyclin is also involved

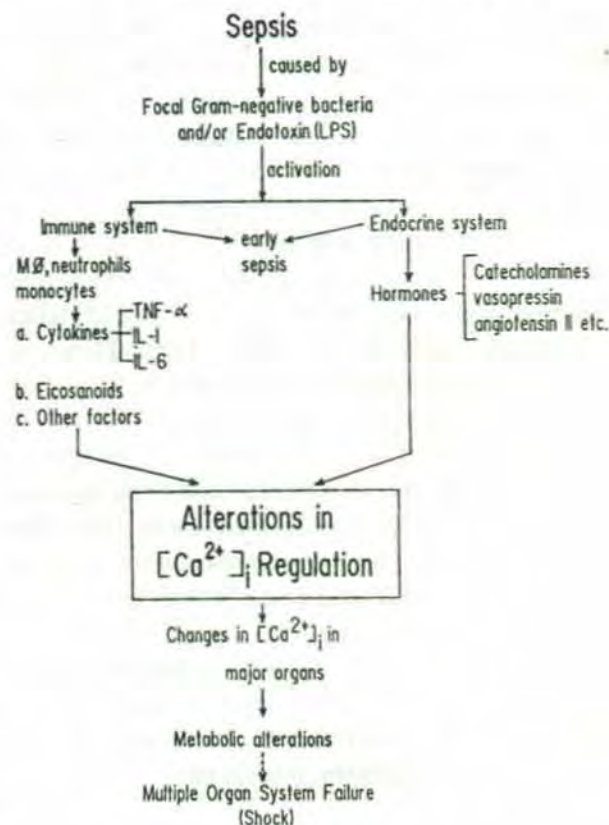


Fig. 1: Schematic representation of the interplay between [Ca²⁺]_i and other mediators during sepsis.

in this process. It is thus suggested that sepsis related endocrine and immune responses cause an alteration in calcium homeostasis and/or signalling in skeletal muscle cells, hepatocytes and T-lymphocytes.

5. Clinical implications

The intracellular function of Ca²⁺ as a coupler of membrane potential- or agonist-activation of cells to vital cellular responses is dependent on discrete Ca²⁺ movements across the plasma membrane. The clinically relevant calcium blockers, verapamil, diltiazem and nifedipine are known to

abrogate intracellular Ca^{2+} -dependent functions, by interfering with trans-membrane Ca^{2+} movement (29). In cardiac and smooth muscle, the antagonists exhibit a use-dependent and voltage-dependent blockade of Ca^{2+} inward current, thus they are most effective in depolarized tissues. For this reason, these antagonists are therapeutically used in cardiovascular diseases such as cardiac arrhythmias, arterial hypertension and some forms of coronary disease. Since Ca^{2+} blockers are known to attenuate agonist- or receptor-operated calcium channel activity in tissues such as smooth muscle and liver (30, 31), they may also play a therapeutic role in disease conditions involving receptor-operated Ca^{2+} channel hyperfunction. Hyperfunction of calcium channels could contribute to altered intracellular Ca^{2+} homeostasis including the so called intracellular calcium overload.

CONCLUSION

Evidence of intracellular Ca^{2+} regulation

in major organs during septic injury in experimental animal models have supported the concept that this regulatory process is altered reversibly in pathophysiologic states. In skeletal muscle specially, increased Ca^{2+} flux results in increased protein catabolic response as well as Ca^{2+} -dependent protease activity. Restoration of the Ca^{2+} regulation by means of calcium channel blockers, could prevent the uncontrolled septic response. Thus calcium channel blockers may be effective as a therapeutic strategy in the treatment of septic disorder. Since septic injury and related metabolic derangements are probably mediated by cytokines (TNF, IL-1 and IL-6) released from infective foci, these immunomodulators may play a role in metabolic modulation in major organs during sepsis.

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