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An elementary analysis of physiologic shock and multi-organ failure: the Autodigestion Hypothesis

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Abstract— **Physiological shock and subsequent multi-organ failure is one of the most important medical problems from a mortality point of view. No agreement exists for mechanisms that lead to the relative rapid cell and organ failure during this process and no effective treatment. We postulate that the digestive enzymes synthesized in the pancreas and transported in the lumen of the small intestine as requirement of normal food digestion play a central role in multi-organ failure. These powerful enzymes are usually compartmentalized in the lumen of the intestine by the mucosal barrier, but may escape into the wall of the intestine if the permeability of the mucosal lining increases. Entry of the digestive enzymes into the wall of the intestine precipitates an autodigestion process as well as an escape of pancreatic enzymes and breakdown products generated by them into the system circulation. The consequence of autodigestion is multiorgan failure. We discuss the possibility to block the digestive enzymes in acute forms of shock as a potential therapeutic intervention.**

I. Introduction

Physiological shock and multi-organ failure have the highest levels of inflammatory markers and mortality found among human diseases. They arise as a consequence of any of a range of complications, be it trauma, burns, loss of blood volume, surgery, or numerous others. Shock and multi-organ failure occur in many different mammalian and non-mammalian species and at any age and thus shock is unlikely a genetic problem., They can occur besides in hospital emergency or intensive care rooms in many other situations and circumstances in life. It may be that many deaths are associated with multi-organ failure.

Following an initial insult, multi-organ failure may arise within hours and linger on for days in a catastrophic sequence of cell dysfunctions and perfusion deficiencies. It is an emergency situation during which organs fail, for example by fluid accumulation in the lung, known as acute respiratory distress syndrome, a lack of urine production due to renal failure, or in form of blood pressure reduction due to cardiac and peripheral vascular failure, to name a few examples. As more organs go into failure the incidence of death raises, and may reach 100% by the time three or more organs have failed.

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II. Mechanisms for shock

In spite of the extraordinary importance, the underlying mechanisms for shock and multi-organ failure are currently unknown and consequently no effective intervention exists. Patients receive supporting therapy but there is no approach to assist the circulation and organ functions with an approach that corrects the course of events at the root of the problem.

There is a long-standing observation that shock involves internal organs and especially the intestine. Since the intestine is exposed to the environment, this has lead in the past to the hypothesis that bacteria or endotoxins derived from the intestine could play a role in the inflammation and consequent organ failure. The idea is that the intestinal barrier formed by the mucosal epithelium becomes permeable and allows cytotoxic products derived from bacteria to enter the circulation, which in turn initiate proinflammatory processes. Although plausible, this idea (designated as endotoxin translocation hypothesis) has been tested in multiple ways in clinical trials and has not lead to effective clinical interventions. While some patients may develop severe forms of bacteremia, in most patients there are other mechanisms at work that can lead to complete organ failure within hours without sufficient time to develop bacterial colonies. Instead there is a need for a fundamental new understanding of this important problem.

III. Autodigestion

We present evidence for a previously untested mechanism due to autodigestion by the digestive enzymes synthesized in the pancreas and carried in the lumen of the intestine as part of normal food digestion [1].The powerful digestive enzymes have the ability to digest within hours almost every biological material. Digestive enzymes (proteases, lipases, amylases, nucleases) are present in the lumen of the intestine in concentrations higher than in other organs and they are relatively nonspecific in their ability to degrade proteins, lipids, carbohydrates and nucleotide polymeric chains. They are designed to generate from biopolymers individual monomeric building blocks for absorption by the epithelium

as nutritional support. Autodigestion of the intestine is prevented by compartmentalizing the fully activated enzymes in the lumen of the intestine by means of the mucosal barrier.

But when the mucosal barrier opens after an initial insult and the permeability of the epithelial barrier increases, digestive enzymes may escape from the lumen into the wall of the intestine [2]. This sets up a condition in which the structures and cells in the wall of the intestine become exposed to autologous digestive enzymes. The consequence is destruction of interstitial structures and cell membrane molecules, including E-cadherin between epithelial cells, thus compromising the tight intestinal barrier properties of the intestine. The digestive enzymes develop unrestricted access to the intestinal wall, cause destruction of the villi thereby eliminating the molecular machinery for food absorption, and may even destroy the intestine smooth muscle thereby compromising the ability of food transport by peristalsis. In addition, the digestive enzymes generate tissue breakdown products, especially lipid fragments (e.g. unbound free fatty acids), which in turn are proinflammatory and if generated in sufficient concentrations are cytotoxic.

As time progresses in shock, the digestive enzymes and the cytotoxic fragments generated by them in the wall of the intestine escape into the central circulation via the portal venous system, the intestinal lymphatics and the peritoneal space. The consequence is a systemic inflammation and cell dysfunctions in peripheral organs, and thus the potential for multiorgan failure.

IV. Defenses against autodigestion

According to this mechanism there are two lines of defense against autodigestion, prevention of breakdown of the mucosal barrier properties in the first place and acute transient blockade of the digestive enzymes as a second line of defense. In many real life shock situations, the breakdown of the mucosal barrier precedes access to a patient. Thus the second line of defense needs to be the main focus of an intervention against multi-organ failure. There may also be opportunities to minimize a breakdown of the mucosal barrier, e.g. in elective surgery.

V. Enteral blockade of digestive enzymes

We tested the hypothesis that inhibition of pancreatic enzymes in the lumen of the intestine may serve to attenuate formation of cytotoxic mediators in ischemic tissues following shock, and consequently prevent cell and tissue injury as well as multi-organ failure. Experiments in a variety of experimental forms of shock with several pancreatic protease inhibitors showed a significant reduction of the destruction of the mucosal barrier, reduced markers for systemic inflammation as well as inflammation in peripheral organs and improved survival rates [3-7]. The idea of blocking digestive enzymes in the lumen of the intestine remains to be tested in patients.

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