Acute phase reactants

Acute phase reaction is a physiological event which manifests by the **system release of inflammation mediators** as a result of the development of pathological processes (inflammation, trauma, surgery, myocardial infarction, birth, cancerous processes, stress, or excessive physical activity). Mediators serve to ensure the complete response of the organism, **communication and regulation** of the ongoing actions. They also cause the **general symptoms** (fever, tiredness, exhaustion, muscle and joint pain). Substances, which get synthesised as a result of a known pathology or whose concentration corresponds to the degree of tissue damage, are clinically significant. These substances are called markers. By assessing them we can confirm or rule out diagnosis of a different disease.

Significance of acute phase reactants

The complex of acute phase proteins is fairly heterogeneous. Regardless, according to their effect, they can be classified into one of the following groups:

Immune reaction components

Some acute phase reactants directly participate in the destruction of the pathogen/noxa that had caused the inflammation. Other proteins play a role in removing damaged cells, or modulating the immune reaction. These are e.g.

- C-reactive protein
- complement components (especially C3 and C4)
- tumor necrosis factor α (TNF-α), interleukin 1 (IL-1), and interleukin 6 (IL-6).

Protection against collateral tissue damage

During the acute phase, phagocytes and disintegrating cells release substances which are supposed to destroy the pathogen that had caused the inflammation, and “dissolve” the damaged tissue. These are mainly proteolytic enzymes and reactive oxygen species. It is necessary to limit the effects of these substances, so that they work where they’re supposed to - aka the collateral tissue damage should be the smallest. Among these reactants, therefore, we can find:

protease inhibitors

- α_1-antitrypsin
- α_1-antichymotrypsin
- α_2-macroglobulin

Proteins which lower the production and availability of reactive oxygen species

These are not only reactive oxygen species scavengers in the truest sense of the word, but also proteins which bind and stabilise transient metals and their complexes. In this way, they lower the production of reactive oxygen species in Fenton’s reaction and similar chemical processes. These are:

- haptoglobin
- hemopexin
- ferritin
- ceruloplasmin

Transport of waste products that get created during inflammation

Besides the aforementioned hemoglobin and hemopexin, there is probably also

- serum amyloid A (SAA)

Coagulation factors and proteins taking part in tissue regeneration, e.g.

- fibrinogen

The significance of some positive acute phase reactants remains **unknown**, even though these may be clinically significant proteins (used as inflammation parameters). Among these we can mention procalcitonin (PCT).

The velocity of concentration changes in acute phase proteins

The plasmatic concentration of different acute phase reactants changes variably fast. Depending on the time since the start of the illness in which it changes, we divide the acute phase reactants into three groups:

Early acute phase proteins

These are proteins with a very short biological half-life. The changes in their plasmatic concentrations are apparent within 6 to 10 hours since the start of the illness. They peak usually during the second or third day. The main representatives are mainly **C-reactive protein (CRP)** and **serum amyloid A (SAA)**. Nowadays, **procalcitonin (PCT)** is used in clinical practice.

C-reactive protein

CRP is one of the most important acute phase reactants. It is a protein playing the role of an opsonin. It got its name from precipitating with a so-called pneumococcal C-polysaccharide. The plasmatic concentration of CRP increases in 4 hours after inducing the acute phase reaction, and during the first two days it rises more than 100x. Maximum concentration is reached within 24-48 hours, and its half-time is also around 24 hours. Physiologically the plasmatic concentration is up to 8 mg/l. A sudden and large increase of CRP (typically over 60 mg/l) follows particularly acute bacterial infections, less commonly also mycotic infections. Viral infections, conversely, are characterised by a relatively low increase of CRP (usually below 40 mg/l). Determining the plasmatic concentration CRP therefore helps to decide whether or not to start antibiotic treatment. A successful antibiotic therapy then shows a fast decrease of CRP, and an increase remains in an unsuccessful one. By determining CRP, it is possible to detect the risk of post-surgery infection. On the third day after surgery, its concentration should quickly fall to normal levels. Lasting increase, or just a partial decrease followed by another increase, implies the presence of an infection or another inflammatory complication. A slight increase in CRP also follows a myocardial infarction. Generally it can be said that mildly elevated levels of CRP (around 10 mg/l) belong among signs of a high cardiovascular risk. Tracking CRP concentrations is useful also in autoimmune disease monitoring. The main disadvantage of CRP is its low specificity. In contrast to procalcitonin it doesn’t inform of the severity of organ damage, but only the presence of an infection. These two parameters aren’t mutually exclusive, but supplemental.

Procalcitonin

In recent years, PCT has started to appear both in research and in clinical practice as an acute phase reactant. This protein, containing 116 amino acids and with the molecular weight 13 000, is physiologically produced by the C-cells of the thyroid gland as a precursor of calcitonin. Mainly during generalised bacterial infections, other cells start to produce it - mainly the neuroendocrine cells of the lungs and intestines, but also the cells of other parenchymatous organs, and during sepsis essentially all types of tissues and cells. The plasmatic concentration of this protein then rises sharply. PCT released during sepsis is not converted to calcitonin. The exact physiological significance of PCT is unknown; it is assumed that it participates in inflammation regulation and has analgesic effects. The half-time of PCT is one day, and after immune stimulation its serum concentration rises during 2-3 hours more than 20x. Increase can also be observed only in generalised bacterial, mycotic, and protozoal infections, it does not show up in virus infections. A less notable increase can be seen in polytraumas, burn injuries, and after extensive abdominal surgeries.

Acute phase proteins with medium response time

These are proteins, the concentration of which changes within 12 to 36 hours since the start of the illness, and reach their peak by the end of the first week. They include α_1-acidic glycoprotein (orosomucoid), α1-antitrypsin, haptoglobin, and fibrinogen.

Late acute phase proteins

They include C3 and C4 parts of the complement and ceruloplasmin. The changes in their concentrations only start after 48 to 72 hours after the start of the illness. The increase of concentrations is less pronounced in comparison to the two previous groups, and they reach their peak only after 6 to 7 days.

Negative acute phase reactants

Negative acute phase reactants are proteins whose concentrations decrease during the acute stage. The main representatives are albumin, prealbumin, and transferrin. They have a lower importance for the observing and evaluation of the load reaction than positive reactants. They are, however, often used as a liver protein synthesis criterium, and as malnutrition pointers.

Links

References