

The molecular basis of procalcitonin synthesis in different infectious and non-infectious acute conditions

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Abbreviations: PCT, Procalcitonin; PAMP, Pathogen Associated Molecular Pattern; IL-1 β , Interleukin-1 Beta; IFN- γ , Interferon Gamma; LRTI, Lower Respiratory Tract Infection; IL-17, Interleukin-17; CPR, Cardiopulmonary Resuscitation; IRI, Ischemia-Reperfusion Injury; DAMP, Damage Associated Molecular Pattern; ICU, Intensive Care Unit

Introduction

Procalcitonin (PCT) has been considered as a suitable tool for early detection differential diagnosis of bacterial infections and also for tailoring antibiotic therapy better¹. However, there are several other factors influencing PCT production apart from bacterial infections only. Understanding the molecular basis of PCT synthesis, which is determined by the interaction between the initiating insult (infections or non-infectious injuries) and the host response summarized in the current review, will help us to the interpret PCT levels at the bedside with a greater confidence²⁻⁴.

PCT synthesis in infections

Bacterial infections: By and large PCT levels are elevated in bacterial infections as reported by several studies, but the feature of the response can be different. For example higher peak PCT concentrations are expected in Gram negative as compared to Gram positive infections. Furthermore, differences may also be seen even within the family of Gram negative bacteria: as higher peak PCT concentrations can be detected in Enterobacteriaceae, as compared to non-fermentative Gram negatives or obligate Gram negative anaerobes.^{5,6} This is due to the polymorphism of the pathogen associated molecular patterns (PAMP) resulting in slightly different cytokine profiles hence different PCT values. In neutropenic patients, as the vast majority of the PCT synthesis is originated from the monocytes and macrophage cells, an attenuated response is expected with lower PCT levels⁷⁻¹¹.

Viral infections: Linscheid and coworkers has shown in differentiated adipocyte cell culture that addition of interleukin-1 beta (IL-1 β) has induced the synthesis of PCT while the addition of IL-1 β and interferon-gamma (IFN- γ) concomitantly has blocked it^{12,13}. In viral infections the host T helper lymphocytes are forced to produce IFN- γ which has a negative feed-back effect on the synthesis of (IL-1 β), which is the main trigger of PCT induction. However, peak PCT concentrations would very seldom reach that of seen in bacterial infections. This is also true for chronic viral infections as can be seen in HIV infections, the peak concentration and the cut-off are considered to be lower^{14,15}. The discriminative effect of the PCT can be used in the clinical practice as described in the French and German

guidelines for the management of meningitis^{16,17} and in the antibiotic reduction in case of lower respiratory tract infections (LRTI)¹⁸, (Figure 1). Nevertheless, it is also important to acknowledge that bacterial super-, or co-infections can facilitate the synthesis of PCT, which makes the interpretation of PCT results more difficult under such circumstances, therefore, detailed clinical and microbiological assessment of the patient is inevitable to make appropriate decisions.

Fungal infections: Initially it was considered in a paper by Huber that PCT has no value in invasive fungal infections^{19,20}. This was based on the finding that the magnitude of PCT elevation was far less than expected. However, more recent results reported that there may be a detectable PCT response in certain cases of invasive fungal infections, although there are substantial differences in the PCT levels found^{5,21,22}. This could be due to the different host response to different Candida species, which should be tested by further studies²³. One of the reasons why PCT concentrations are lower in fungal infections than in bacterial infections is the increased synthesis of IFN- γ and IL-17 as part of the intact immune response for fungal infections, both of which are able to decrease/block the induction of PCT synthesis²⁴. In cases of mixed bacterial-fungal infections, often seen in intensive care patients, we face similar diagnostic difficulties as discussed in the previous paragraph. As the blocking effects of IFN- γ and interleukin-17 (IL-17) on PCT production can be overwhelmed by host's response for bacterial super-infection, PCT synthesis can be detected but the magnitude may be lower than seen in bacterial infection only. To overcome this diagnostic challenge the complex

evaluation of PCT levels with fungal infection markers such as β -D-glucan, galacto-mannan and combining it with the Candida score is recommended²⁵.

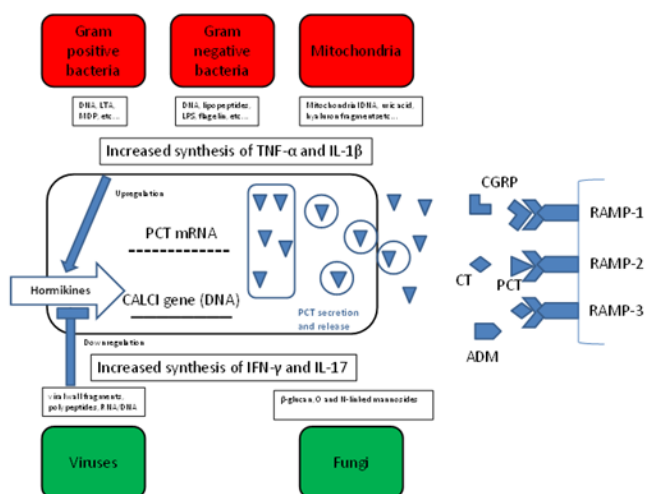


Figure 1 Schematic pictures of PCT induction in different infectious and non-infectious conditions and the receptorial interaction between the CALC gene family proteins.

DNA: Desoxy-Ribonucleic Acid; LTA: Leukotrien A; MDP: Metal-Dependent Phosphohydrolase; LPS: Lipopolysaccharide; TNF- α : Tumor Necrosis Factor Alpha; IL-1 β : Interleukin-1 Beta; PCT: Procalcitonin; CALCI Gene: Calcitonin I Gene; IFN- γ : Interferon Gamma; IL-17: Interleukin-17; RNA: Ribonucleic Acid; CGRP: Calcitonin Gene Related Protein; CT: Calcitonin; ADM: Adrenomedullin; RAMP-1, 2, 3: Receptor Activity-Modifying Protein 1, 2, 3.

Non-infective causes of PCT elevation

Unspecific PCT elevations can also be found in the absence of infection^{26,27}. In medical patients, non-specific PCT elevations can be seen due to several reasons. For example in some malignancies like the small cell lung carcinoma, bronchial carcinoma, the C-cell carcinoma of the thyroid gland and neuroendocrine tumors of the gastrointestinal system PCT can be elevated^{28,29}. Medications, like anti-thymocyte-globulins used in transplantation medicine also can induce a cytokine storm with the consequence of PCT mono-induction³⁰. In cardiogenic shock³¹, cardio-pulmonary resuscitation (CPR)³², sterile pancreatitis³³ and rhabdomyolysis due to the ischemia-reperfusion injury (IRI) induced damage associated molecular pattern (DAMP) substantial PCT increase can be detected³⁴. After surgery a DAMP initiated PCT mono-induction are very often present, with its peak on the first or second post-operative days followed by a gradual decrease thereafter.³⁵

In surgical patients with early infectious complications, DAMP and PAMP take place in a parallel fashion resulting in a synergistic effect on the inflammatory response and a re-induction of PCT production will take place resulting in an increasing or “not-decreasing” tendency of the daily PCT levels. If infectious complications occur at a later stage of the patients’ ICU stay, PCT will increase again but the absolute values may be lower as if it had happened during the early stage, although the clinical significance (i.e.: the severity of the infection) may be just as severe. Although medical and surgical patients are different as far as the inflammatory response, hence the PCT absolute values are concerned, but changes in the kinetics of PCT, i.e., interception of decreasing kinetics or in fact a sudden increase may carry invaluable information and helps the clinician to change course of treatment early.³⁶

Conclusion

Procalcitonin is very useful marker in the critically ill, but single cut-off values are very difficult to define as it is affected by several confounding factors. However, the dynamics of PCT values may provide a more relevant information about the onset of bacterial infections and potentially could be used in assisting antimicrobial therapy. In viral and fungal infections evaluation is more difficult, but with careful assessment of the patients’ medical history, current complaints, results of the diagnostic tests and combining these with PCT values may have some merit, which may also serve as a very interesting research topic for the future.

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None.

Conflicts of interest

None.

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