

Physiology of the inflammatory response: the time course as a guide for anti-inflammatory intervention.

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The use of non-steroidal anti-inflammatory drugs (NSAIDs) is very common in our society. Besides the fact that they are prescribed for a wide range of diseases, the population frequently use them in an indiscriminate fashion. Although these drugs can reduce the symptoms of the inflammatory process, they can cause side effects that eventually counterweight its own benefits. Here, we will discuss how dentists should decide the best time point to prescribe anti-inflammatory drugs considering the time course within the onset and the resolution phase of the inflammatory process.

Inflammation is a stereotyped response, inherent to vascularized tissues, which has the objective of reestablishing tissues homeostasis. The inflammatory process has cellular and humoral components, such as leucocytes (neutrophils, macrophages, eosinophils, mast cells and lymphocytes) and the humoral proteolytic systems (complement, kinins and coagulation), respectively. These components work synergistically and simultaneously, causing vascular alterations and leukocyte recruitment to the lesion. Leucocytes (initially neutrophils), begin to phagocytose bacteria and cellular debris, performing a primary clearance of the lesion. The peak of neutrophil recruitment is followed by the arrival of macrophages into the tissue, which phagocytose the remaining cellular and bacterial residues, including apoptotic neutrophils [1]. At the same time, lymphocytes can be activated in the lymph nodes by antigen-presenting cells (e.g., dendritic cells) from the tissue, initiating the production of antibodies by B cells and the migration of T helper lymphocytes to the inflamed site. Following the course, stromal and parenchymal cells multiply and reconstitute the tissue, whilst most of the remaining macrophages and lymphocytes leave through the lymphatics.

Inflammation is essential for the survival of the host, but is accompanied by its classical cardinal signs rubor, calor, tumor and dolor (redness, heat, tumor and pain), which are the main cause of patient discomfort, especially after surgical procedures. This impels health professionals to prescribe anti-inflammatory drugs, a practice that should be restricted to the shortest period possible following the patient's lesion or surgical intervention. The reason for that is the mechanism of action of NSAIDs, which is the inhibition of the enzyme cyclooxygenase (COX) which takes part in the synthesis of pro-inflammatory lipid mediators known as prostaglandins and thromboxanes. Ironically, the same mediators that induce the initial phase and symptoms of inflammation are those who will take part and stimulate the expression of other enzymes that synthesize mediators responsible for the resolution of inflammation, or in other words, its end. For example, prostaglandin E2 (PGE2) and prostaglandin D2 (PGD2) induce the expression of the enzyme 15-lipoxyge-

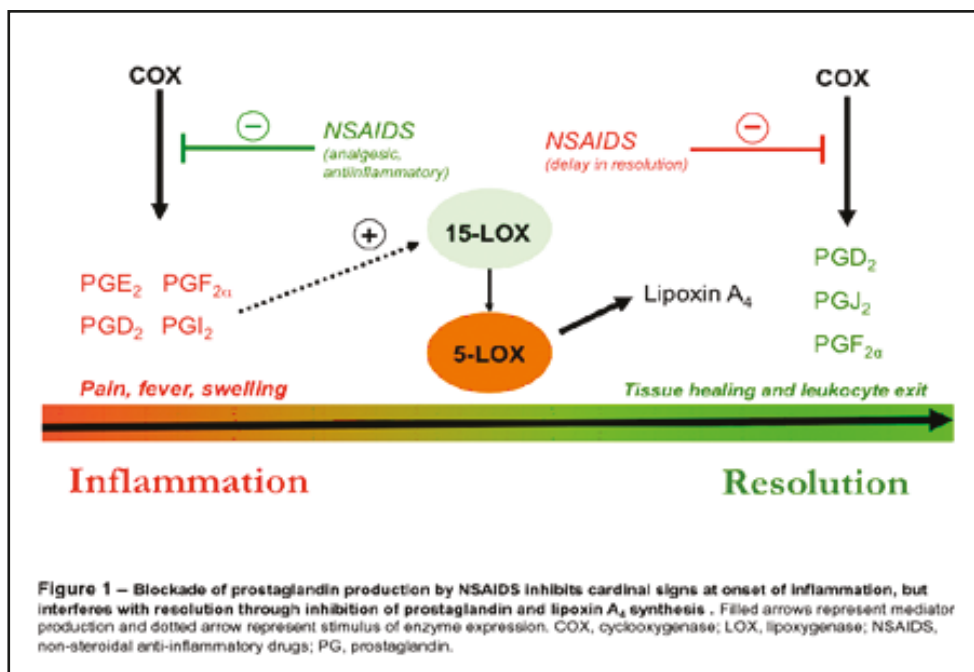
nase (15-LOX) in its active form in leucocytes, which catalyzes a step in the production cascade of a potent pro-resolving mediator named lipoxin A4 [2]. One of the pathways for this pro-resolving mediator production is the consecutive action of 15-LOX and 5-LOX in mucosal tissues, shown in FIG. 1, a process which deserves special attention by dentists.

Lipoxin A4 is a member of a group of lipid mediators of resolution that includes resolvins, protectins and the aspirin-triggered analogs of these classes. It does not have immunosuppressive properties, in contrast, it activates specific cellular mechanisms, such as the stimulation of non-phlogistic recruitment of monocytes (that is: without elaborating pro-inflammatory mediators), activation of macrophage phagocytosis of microorganisms and apoptotic cells, increase in phagocyte exit through the lymphatics, expression of antimicrobial molecules and inhibition of further neutrophil and eosinophil infiltration [3].

Another interesting resolution pathway, whose discovery created a lot of controversy in this field of research, is the action of prostaglandins at the resolution phase of inflammation [4]. It was demonstrated that COX is expressed also at that time, correlating with the production of PGD2, prostaglandin 15-deoxy- $\Delta^{12,14}$ -PGJ2 (15d-PGJ2 - the non-enzymatic degradation product of PGD2) and recently, prostaglandin F2 α (PGF2 α). While data confirming PGF2 α resolution properties is limited, PGD2 and 15d-PGJ2 have well established anti-inflammatory and pro-resolving effects on inflammation models, such as promotion of leukocyte apoptosis, macrophage clearance from inflamed sites, and control of cytokines and chemokines that regulate leukocyte trafficking. These effects are mediated by activation of DP1 receptor by PGD2 and inhibition of nuclear factor γ B (NF γ B) activation through peroxisome proliferator-activating receptor γ (PPAR γ) by 15d-PGJ2 [5].

Considering all this information, which is summarized in FIG. 1, the prolonged or delayed use of anti-inflammatory drugs, by blocking the production of prostaglandins and the further synthesis of proresolving mediators, could cause a delay in tissue healing or even establishment of a chronic lesion. Some measures can be taken to avoid harming the patients, such as reducing the prescription and use of NSAIDs to the smallest period necessary for symptom relief, for example, edema and pain. In addition, the choice of a medicine with little anti-inflammatory activity but still good analgesic effect, such as acetaminophen (paracetamol), dypirone and diclofenac, or even codeine-NSAIDs combined drugs, should also be considered.

Special attention must also be given to determine precisely the stage of the inflammatory process encountered in the patient before the administration of any kind of anti-inflammatory drug. Knowing the stage of inflammation, the choice of applying drugs with anti-inflammatory activity or only analgesic activity is easier. Proceeding this way, it is more likely that the pharmacological intervention will not interfere with the natural course of inflammation and resolution, therefore, increasing the efficiency in patient treatment and recovery.



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