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The Cardiovascular Effect of the Platelet Activator Factor

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Platelet activating factor (PAF) is one of the most potent mediators found in mammals. PAF is a phospholipid with diverse and potent physiological effects; it is a mediator of cell – to cell communication, which may function either as a intercellular and an intracellular messenger. PAF is produced by a variety of cells, such as monocytes/macrophages, polymorphonuclear and platelets [1]. It has been shown that PAF is released by human endothelial cells after stimulation with several inflammatory mediators, as well as by cardiac tissue after a period of ischemia. The synthesis and the catabolism of this substance are highly regulated. PAF production occurs through two different pathways. The so-called "*remodelling pathway*" is mainly involved in its synthesis by inflammatory cells. The production of PAF requires the activation of phospholipase A_2 and acetylcholine–transferase. The action of the phopholipase A_2 determines the hydrolysis of the membrane phospholipid to generate a 2-lysophospholipids (lyso – PAF), that is the substrate for the acetylcholine-transferase, to obtaine the final product, PAF. The second biosynthetic pathway, "*de – novo synthesis"*, is mainly operative in the kindney and in the central nervous system; this mechanism involves the synthesis of 1–*O*–alkyl–2 acetylglycerol, which is then converted to PAF by a specific choline-phosphotransferase [2] .

The enzyme for the catabolism is a PAF specific acetyl–hydrolase (PAF- AH), that produces the biologically inactive form, lyso – PAF, which posseses a short acyl chain at the 2 *sn* position. This enzyme is present in plasma and in various tissues; in the human plasma PAF-AH circulates as a complex with low (LDL) and high density lipoproteins (HDL) [3]. PAF acts via specific receptors on the membranes of responsive cells. In the human platelets are present two binding sites, different for the affinity and the number sites/platelets. In fact, one binding site presents low capacity of site/platelets, with a high affinity. The second binding site shows an infinite binding capacity, with a low affinity for PAF. The PAF receptor contains 342 amino acids, coupled to a G protein. The signal trasduction of PAF determines activation of phospholipase C and a transient production of diacylglycerol, which in turn activates the protein kinase C pathway, leading to the synthesis of inositol triphosphate and release of calcium by the internal stores. PAF stimulates tyrosine phosphorylation of several proteins in platelets, neutrophils and macrophages, induces stimulation of NF*k*B and the transcription of c-fos and c-jun genes in the inflammatory cells [4].

In the cardiovascular system, PAF induces marked haemodynamic and inotropic effects. Infusion of PAF into the coronary circulation induces variation in the coronary vascular tone depending on the doses and the animal species used. The effects caused by PAF are dose–dependent; at high doses, in particular, PAF strongly reduces coronary blood flow, systemic blood pressure and causes S-T segment depression, a sign of cardiac ischemia. The alteration in the cardiac function induced by PAF include: reduction in cardiac output, due to a direct action on the heart (negative inotropic effect) and indirect effects such as changes in pre- and after- loads pressures. These alterations in cardiac performance may depend on the effects of PAF on the coronary circulation, on the conduction system and on the contractile properties of the heart [5]. A schematic diagram summarising the effects of PAF is reported in figure 1.

The role of PAF during ischemia and reperfusion (I/R) injury of the heart has been evaluated by different Authors. Myocardial synthesis of PAF has been determined in different animal species (*i.e.* in baboons and in the sheep) following myocardial infarction, as well as in humans with coronary disease undergoing atrial pacing. The isolated heart was used as a model to demonstrate the cardiac origin of PAF, which is released in significant amounts during the early phases of reperfusion from ischemic heart [4].

References

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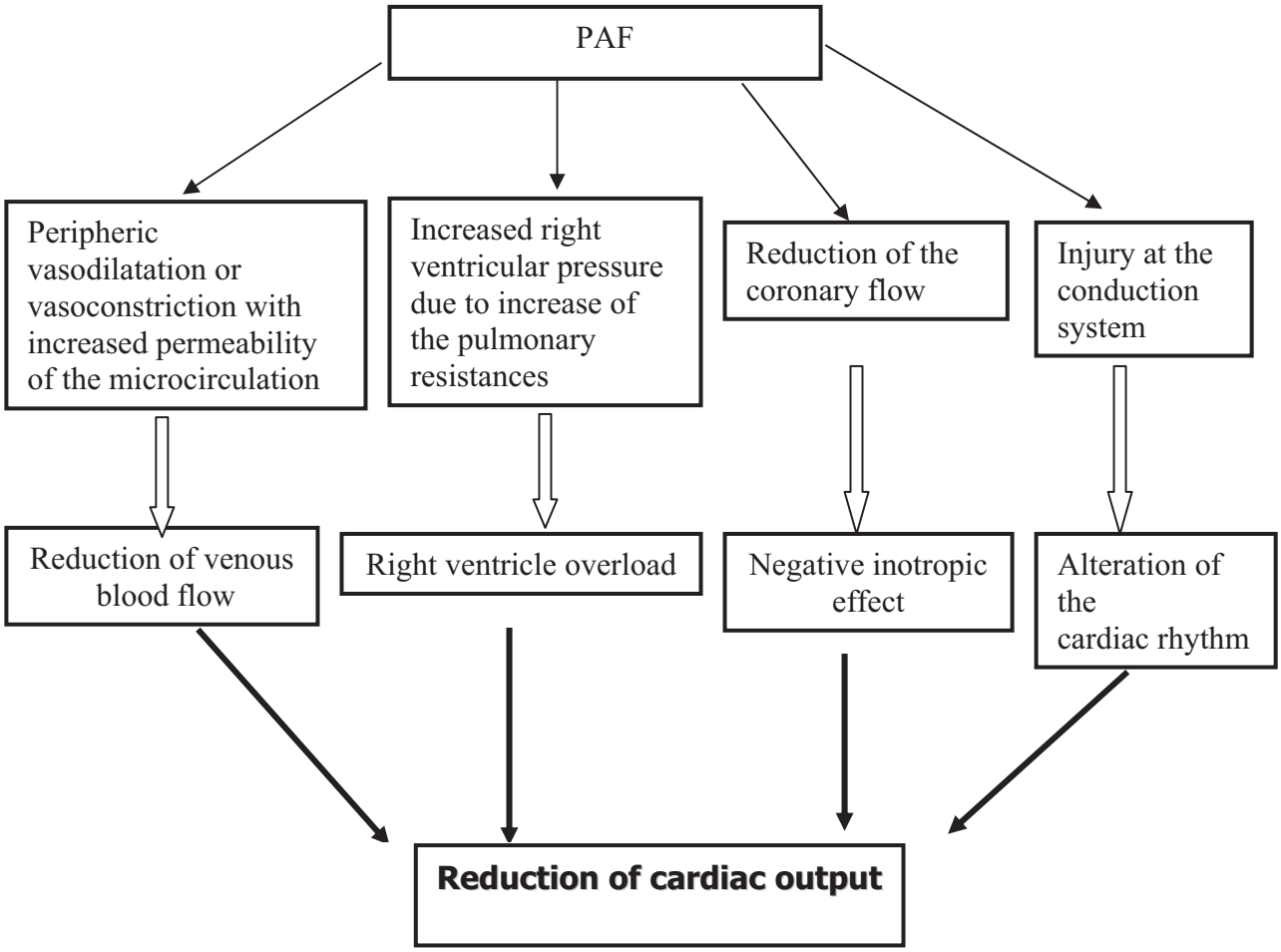

Fig. 1 Schematic diagram summarising the cardiovascular effects of PAF