



2016

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### **Recommended Citation**

Altura, B. M., Shah, N. C., Shah, G. J., Pérez-Albela, J. L., & Altura, B. T. (2016). Insights into the possible mechanisms by which platelet-activating factor and PAF-receptors function in vascular smooth muscle in magnesium deficiency and vascular remodeling: Possible links to atherogenesis, hypertension and cardiac failure. *International Journal of Cardiology and Research*, 3(1e), 1-3.

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## Insights into the Possible Mechanisms By Which Platelet-Activating Factor and PAF-receptors Function in Vascular Smooth Muscle in Magnesium Deficiency and Vascular Remodeling: Possible Links to Atherogenesis, Hypertension and Cardiac Failure

Editorial

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**Keywords:** PAF; Sphingolipids; Atherosclerosis; Hypertension; Cardiac Failure; Ceramide.

### Introduction

Platelet-activating factor (PAF) is a phospholipid mediator and cell signaling molecule which displays multiple biological and pathophysiological attributes, running the gamut from inflammation to cell differentiation and proliferation [1-4]. As is well-known, PAF interacts with specific membrane PAF-receptors (PAF-Rs) to initiate all cellular responses via specific G-protein-coupled receptors [1-4]. Although these initiated membrane receptor phenomena are mostly established for several tissue-cell systems [1-8], exactly how PAF and PAF-Rs cause vascular remodeling in hypertension and atherosclerosis is not clear. A little more than 15 years ago, PAF was identified as a molecule that stimulated activation of nuclear factor-kappaB (NF-kB) [1, 2, 8].

### NF-kB, magnesium deficiency, PAF and sphingolipids

NF-kB is now known to be a prime regulator of growth processes, differentiation, cell migration, and cell death [for reviews, see [9-12], all factors required for vascular remodeling in hypertension and atherosclerosis [13, 14]. NF-kB is clearly a major transcription factor and a pleiotrophic regulator of numerous genes involved in inflammatory processes and epigenetic phenomena [9-12, 15]. NF-kB is now thought to be a pivotal molecule in atherosclerosis, hypertension, cardiac failure and stroke [14-19]. As of now,

it is still not clear as to what factor(s) initiates expression of these molecular events. We were the first laboratory to suggest and provide evidence for a role for activation of NF-kB in the cardiovascular manifestations, particularly atherosclerosis, noted in magnesium deficiency (MgD) [20-22]. We demonstrated that when vascular smooth muscle (VSM) cells were exposed to low concentrations of extracellular, ionized Mg ( $[Mg^{2+}]_o$ ), a concentration-dependent upregulation of NF-kB took place; the lower the  $[Mg^{2+}]_o$ , the faster and greater the upregulation of NF-kB [20-22]. A similar situation appears to have been reported for endothelial cells [23]. Recently, we have reported that lowering  $[Mg^{2+}]_o$  also results in a synthesis and release of activated PAF [24] concomitant with an upregulation of five major sphingolipid enzymatic pathways responsible for formation of ceramide and sphingosine, prior to NF-kB upregulation [18, 20, 21, 24-31].

### Magnesium deficiency and activation of sphingolipid pathways in cardiovascular tissues and cells

The *de novo* synthesis of sphingomyelin is brought about via the action of serine palmitoyl-CoA transferase (SPT), 3-ketosphinganine reductase, ceramide synthase (CS), dihydroceramide desaturase, and SM synthase (SMS; ref [32]). SMS requires phosphatidylcholine (PC) and ceramide as substrates to manufacture SM and diacylglycerol (DAG; see ref. [32]). This reaction directly affects SM, PC, and ceramide as well as DAG levels

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**Received:** February 18, 2016

**Published:** February 22, 2016

**Citation:** Altura BM et al., (2016) Insights into the Possible Mechanisms by Which Platelet-Activating Factor and PAF-receptors Function in Vascular Smooth Muscle in Magnesium Deficiency and Vascular Remodeling: Possible Links to Atherosclerosis, Hypertension and Cardiac Failure. *Int J Cardiol Res.* 3(1e), 1-3. doi: <http://dx.doi.org/10.19070/2470-4563-160001e>

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in cells. Two of us [21, 33] have previously noted, using primary cerebral, coronary, and peripheral VSM cells in culture, as well as intact ventricular and atrial myocardial muscle obtained from rats after 21 days of short-term MgD [25-37], that variation of  $[Mg^{2+}]_0$  influences the cellular levels of SM, PC, DAG, sphingosine, and ceramide. Our *in vitro* and *in vivo* studies clearly demonstrated that low  $[Mg^{2+}]_0$  resulted in cellular synthesis and release of ceramide due to upregulation of SPT 1 and SPT 2, CS, SMS synthase, and a "salvage pathway" [25-31]. Ceramide is now thought to play important roles in fundamental pathophysiologic processes such as cell proliferation, membrane-receptor functions, angiogenesis, atherogenesis, immune inflammatory responses, cell adhesion, programmed cell death (i.e., apoptosis), and senescence among other functions [18, 25-31, 33-39]. It should be recalled, here, that MgD environments, both *in vivo* and *in vitro*, have repeatedly been shown to produce arterial and arteriolar contraction, vasospasm and vascular remodeling [18, 20, 22, 40-51], which we have demonstrated to involve ceramide (and other sphingolipids), PAF, cellular entry and intracellular release of free  $Ca^{2+}$ , and activation of PKC isozymes, mitogen-activated protein kinases (MAPKs), MAPK kinases, tyrosine protein kinases, P-I-3 kinases, and PAF among other cellular signaling molecules [18, 24, 33, 40-51].

### PAF, magnesium deficiency, ceramide, and activation of proto-oncogenes

The proto-oncogene families, particularly c-fos and c-jun, are two principal players in regulation of cell growth, differentiation, cell migration, and cell death; all important factors in vascular remodeling, as particularly observed in at herogenesis, hypertension, and cardiac failure [11, 13, 14]. It is, however, not clear how these proto-oncogenes are activated in vascular disease processes. Approximately 15 years ago, we discovered that low  $[Mg^{2+}]_0$  resulted in upregulation of both c-fos and c-jun in several types of VSM cells; the lower the  $[Mg^{2+}]_0$ , the faster and the greater the magnitudes of the upregulation of these two proto-oncogenes [22]. In addition, we found that rats given diets reduced in Mg for 21 days resulted in upregulation of c-fos and c-jun in ventricular and atrial myocardial muscle cells [29]. Reduction in extracellular calcium levels resulted in inhibition of these events [22]. Very recently, we reported that exposure of several types of primary cultured VSM cells, from at least three different mammalian species, to low  $[Mg^{2+}]_0$  promoted synthesis and release of PAF and ceramide prior to upregulation of the proto-oncogenes [24]. In very recent experiments, we found that use of several different, specific antagonists of PAF-Rs attenuated, greatly, the PAF-stimulated formation of the proto-oncogenes and ceramide in several types of primary cultured VSM cells, pointing to a novel, new pathway in MgD [[24]; unpublished findings].

### Conclusions

We believe our new findings on PAF, proto-oncogenes, and sphingolipids, e.g, ceramide and sphingosine, probably point to fundamental roles for the upstream regulation of both proto-oncogenes and sphingolipids in both VSM and cardiac muscle cells. These new, exciting findings probably will also be helpful in explaining many of the known cardiovascular manifestations of MgD, particularly vascular remodeling seen in atherosclerosis and hypertension. Last, but not least, our new studies should be useful in future studies designed to counteract many of the

cardiovascular manifestations of MgD.

### Acknowledgments

Some of the original studies mentioned in this report were supported, in part, by Research Grants from The National Heart, Lung and Blood Institute, The National Institute on Drug Abuse, The National Institute on Mental Health and The National Institute on Alcoholism and Alcohol Abuse awarded to B.M.A. and B.T. A.

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