Sphingosine-1-phosphate in the circulatory system: Cause and therapeutic target for vascular dysfunction?

Rudolf Schubert*

University of Rostock, Institute of Physiology, PSF 100888, D-18055 Rostock, Germany

Received 3 February 2006; accepted 9 February 2006

Available online 23 February 2006

See articles by Scherer et al. [6] (pages 79–87) and Ochi et al. [12] (pages 88–96) in this issue.

Small arteries play an important role for blood pressure regulation and blood flow distribution to different organs. The diameter of these vessels is under the control of a number of factors such as blood pressure, flow, conducted signals from neighboring vessel segments, diverse metabolites produced from surrounding tissues, transmitters liberated from nerve endings, substances released from the endothelium, and a variety of vasoactive compounds washed ashore by the blood stream. Among these factors, increasing attention is now being given to bioactive sphingolipid metabolites, especially sphingosine-1-phosphate (S1P).

A number of comprehensive reviews have summarized the current knowledge about S1P (for example, [1–4]). Briefly, S1P plays an important role in such diverse processes as cell migration, growth, shape change, survival, and apoptosis. This allows S1P to contribute to different pathological conditions, for example transplant rejection, sepsis, cancer, immunity, wound healing, and ischemia/reperfusion as well as restenosis, angiogenesis, vascular permeability, and vasospasm. S1P is derived from membrane phospholipids by enzymatic breakdown of sphingomyelin upon cell stimulation. The amount of available S1P is regulated by its synthesis by sphingosine kinase and its degradation by S1P phosphatase or S1P lyase. S1P is a normal component of blood plasma, present at concentrations between 0.2 and 0.5 μmol/L. The concentration of S1P in serum is even higher because it is stored at high concentrations and is thought to be released from platelets and other blood cells as well as high-density lipoprotein. Thus, S1P is in an effective position to regulate the function of the cells in the vascular wall. The effects of S1P are mediated by two pathways. The historically older suggestion was that S1P acts as an intracellular second messenger. Unfortunately, the direct intracellular targets for S1P are not definitively identified. More is known about the effect of extracellular S1P that binds to a family of five G-protein-coupled receptors, S1P1–5 (for more information see [5]) and probably to some other less well-characterized receptors.

Interestingly, S1P has been shown to regulate the contractility of a variety of vascular tissues, causing vasoconstriction in most vessels (for details see reviews [3,4]). It is noteworthy that S1P seems to be more important for the contractile function of small, resistance-type vessels than of conduit vessels. Thus, effects of S1P on blood vessel contractility may have pathophysiological relevance under conditions characterized by increased S1P concentrations. Therefore, S1P and the S1P-activated signalling pathways are potential therapeutic targets for the treatment of, for example, hypertension, stroke, and vasospasm. However, the understanding of the relationship between the vasoactive mechanisms and the pathophysiological role of S1P in vascular tissue is still limited, mainly because studies on this relationship in functionally important small arteries are scarce.

It is the merit of the study by Scherer et al. [6] published in this issue of Cardiovascular Research to provide new evidence for the potential pathophysiological relevance of the action of S1P on small arteries. The authors show that mRNA transcripts encoding sphingosine kinase, S1P phosphohydrolase, and three S1P receptors (S1P1–3) are present in the gerbil spiral modiolar artery. Thus, at the mRNA level, all necessary components of the
S1P signalling pathway are expressed for S1P to act as an endogenous regulator of spiral modiolar artery tone. Indeed, S1P induces a concentration-dependent constriction of the spiral modiolar artery with an EC50 of 115nmol/L, which is close to the reported plasma concentrations. The constriction is accompanied by an increase of the apparent calcium sensitivity of the contractile apparatus. The Rho kinase inhibitor Y27632 reversed the S1P-induced vasoconstriction and the increase of calcium sensitivity. This finding shows that Rho kinase is active in arteries exposed to S1P. In addition, RhoA, the activator of Rho kinase, translocates to the plasma membrane in response to stimulation with S1P. Thus, the presence of active RhoA and Rho kinase in arteries exposed to S1P is most likely due to a S1P-induced activation of the RhoA/Rho kinase pathway.

The present investigation extends previous reports of the same group on the S1P–RhoA/Rho kinase pathway. In these studies, conducted on small arteries from hamster gracilis muscle, it was shown that exogenous S1P induces constrictions without changing the intracellular calcium concentration [7] and that endogenous S1P contributes to both major components of the mechanism of the myogenic response: the initial increase of the intracellular calcium concentration and the increase of the calcium-sensitivity of the contractile apparatus [8].

Along with the evidence for the pathophysiological relevance of the ability of S1P to affect the contractility of the gerbil spiral modiolar artery, the study by Scherer et al. [6] points to several additional important issues. Firstly, the gerbil spiral modiolar artery was observed to have an extensive length. Thus, the pressure in the vessel will drop over a long distance. As a result, a large change in pressure, and consequently in blood flow, will be obtained at the distal end of the vessel even with small changes in vessel diameter. In this case, a vasoactive compound does not have to be exorbitantly potent or released at high concentrations by pathologically relevant mediators. Secondly, the functional state of blood vessels is considered classically to be regulated by a simultaneous change of the intracellular calcium concentration and the calcium sensitivity of the contractile elements. Historically, the importance of changes in calcium sensitivity were recognized later, but now a number of mechanisms controlling the calcium sensitivity of the contractile apparatus have been described [9, 10]. Thus, it is noteworthy that the S1P-induced constriction of the small gerbil spiral modiolar artery documented by Scherer et al. [6] is dominated almost completely by a change in the calcium sensitivity of the contractile apparatus. Thirdly, as mentioned above, the effects of S1P are suggested to be mediated by two pathways, S1P acting as an intracellular second messenger and S1P binding to G-protein-coupled receptors. It is tempting to speculate that the transient increase in the intracellular calcium concentration and the activation of the RhoA/Rho kinase pathway demonstrated in the present study by Scherer et al. [6] reflect the activation of the intracellular and extracellular pathways, respectively. The data presented seem to indicate that the extracellular pathway dominates the contractile effect. Nevertheless, it will be an interesting challenge to address the question of the functional relevance of the S1P-induced transient increase of the intracellular calcium concentration. Thus, it is still not clear how the intracellular and the extracellular pathways are orchestrated. In this context it should also be clarified whether S1P is a constitutively present, tonically active factor or an inducible factor that acts only when needed. Fourthly, the pathophysiological relevance of the work by Scherer et al. [6] is not only based on the observation of a potent action of the potential pathophysiologically important substance S1P, but also on the finding that the RhoA/Rho kinase pathway mediates its effect. Indeed, in small arteries it has been observed that the RhoA/Rho-kinase pathway is activated in several cardiovascular diseases and may serve as an important therapeutic target in cardiovascular medicine [11]. It will be the aim of future studies to decide whether RhoA/Rho kinase or S1P/S1P kinase/S1P phosphatase are the more promising targets for therapeutic interventions.

Last but not least, it should be mentioned that in this issue of Cardiovascular Research Ochi et al. [12] reported that S1P stimulates an inward-rectifying potassium current in guinea pig atrial myocytes leading to a shortening of the action potential. This effect may be relevant for atrial rhythm disturbances and provides additional evidence for the importance of S1P in the cardiovascular system.

References


