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COMMENTARY

IMPROVEMENT OF TISSUE PERFUSION WITH INHIBITORS OF CALCIUM ION INFLUX

J. M. VAN NUETEN* and P. M. VANHOUTTE†

*Department of Pharmacology, Janssen Pharmaceutica, Beerse, and †Department of Medicine, Universitaire Instelling, Antwerpen, Wilrijk, Belgium

The normal functioning of the body cells requires an appropriate supply of oxygen and substrates, and the continuous wash-out of metabolites (e.g. carbon dioxide and lactate). This is achieved in the intact organism by continuous matching of the amount of blood delivered to the tissues with their metabolic needs. Thus, when the demands are increased, the arterioles branching into the capillaries subserving the active cells dilate, allowing for a greater blood flow. If this does not occur, tissue ischemia and dysfunction are unavoidable, and the symptoms of vascular insufficiency follow [25].

From Poiseuille's work of rigid tubes we know that the flow (F) through such a tube is determined by the perfusion pressure (P) and the resistance to flow, according to equation (1)

$$P = F \times R. \quad (1)$$

The resistance (R) to flow is directly related to the length (L) of the tube and the viscosity (η) of the fluid flowing through it, but is inversely related to the fourth power of the radius (r) of the tube, according to equation (2)

$$R = \frac{8}{\pi} \cdot \frac{L \cdot \eta}{r^4}. \quad (2)$$

If a tube is narrowed, its resistance increases and, for a given pressure along the tube, more energy will be required to overcome the increased resistance, and the pressure downstream of the constriction will be lower than if the tube was the same diameter over its total length. When extrapolated to the human cardiovascular system, Poiseuille's work implies that, provided the pressure generated by the heart is maintained at an appropriate level by the cardiovascular reflexes, the amount of blood delivered to each tissue will depend upon the resistance to flow it offers and thus mainly on the diameter of its blood vessels and the viscosity of the blood [25]. Both a decrease of diameter of the arteries and their branches and an increase in blood viscosity can result in insufficient perfusion of the tissues.

Decrease in vascular diameter

In normal conditions, the major determinant of vascular resistance is the degree of opening of the arterioles (resistance vessels). When a tissue becomes metabolically active or ischemic, the accumulation of metabolites causes dilatation of the arterioles both by inhibition of the myogenic activity of the vascular smooth muscle cells in their wall [4, 10, 14, 19, 24] and by prejunctional inhibition of the existing sympathetic tone [18]. If the distending pressure in the arterioles decreases at the same time, the reduced wall stress will enhance the vasodilatation (autoregulation; e.g. [16, 28]). There is no evidence that the potential of resistance vessels to dilate is curtailed in abnormal conditions. However, pathological decreases in diameter can occur in larger arteries. Such decreases can be due to mechanical obstruction, as is the case with thrombosis, embolization, occlusive disease (atherosclerosis) or external compression. They can also be provoked by spasms of the smooth muscle cells in the vessel wall, as evidenced best by the spastic episodes in patients with Raynaud's disease [23], or by the coronary vasospasms in patients with variant angina [15]. In the latter case, it is likely that vasospasm occurs most frequently in partially occluded blood vessels and thus further impairs the limited blood supply [25]. Whether due to mechanical factors or to spasm, the decrease in arterial diameter results in an exaggerated drop in pressure across the obstruction. Thus the perfusion pressure at the arteriolar level is lower than normal, and despite the normal response of their arterioles, the tissues past the obstruction cannot be provided with enough blood, particularly if their demands are augmented. This situation causes the typical symptoms of angina pectoris or intermittent claudication.

Vasospasm is due to contraction of vascular smooth muscle cells. These are triggered either by the presence of higher than normal levels of endogenous vasoconstrictor substances (e.g. norepinephrine, 5-hydroxytryptamine, certain prostaglandins, thromboxane A_2), by the augmented breakdown of endogenous vasodilator substances (e.g. adenosine, bradykinin, prostacyclin) or by an abnormally high sensitivity of the smooth muscle cells to normal levels of vasoactive agonists (e.g. Raynaud's disease). Thus vasospasms can be provoked by the imbalance between endogenous vasodilator and vasoconstrictor substances or by the interaction between such substances [2, 30]. Sustained contraction of vascular smooth muscle cells can also be evoked in the presence of low concentrations of vasoconstrictor substances by decreases in temperature or by tissue anoxia [31–33]. Ultimately, all stimuli causing vascular smooth muscle to contract, increase the cytoplasmic concentration of activator calcium ions (Ca^{2+}). In most arteries,

the influx of extracellular Ca^{2+} is also augmented since the cellular stores of this ion mediate only part of the contractile response [5, 6, 26, 27]. A number of substances, including cinnarizine, flunarizine, verapamil, lidoflazine, perhexiline and prenylamine, inhibit the influx of Ca^{2+} into vascular smooth muscle cells [12, 13, 34–36]. They also antagonize the contractions of vascular smooth muscle cells caused by anoxia ([31], Van Nueten, unpublished observations). In pathological conditions where vasospastic episodes contribute to the tissue ischemia, inhibitors of Ca^{2+}-influx must have a beneficial effect. Flunarizine does not affect the myogenic activity of vascular smooth muscle but inhibits the stimulated Ca^{2+}-influx in a variety of blood vessels at concentrations which have no negative inotropic effect on the myocardium [35, 36]. Hence, it is to be expected that substances such as flunarizine will be particularly effective in preventing vascular spasms due to the presence of abnormally high levels of vasoconstrictor substances.

Blood viscosity

In normal conditions, the apparent viscosity of the blood is determined mainly by the concentration of plasma proteins, in particular fibrinogen, and by the number of the red blood cells and their deformability [25]. Hyperviscosity of the blood has been proposed to be one of the major factors resulting in peripheral circulatory disturbances [9, 11, 29]. The extreme example of increases in viscosity resulting in cessation of capillary flow is provided by patients with high levels of cold agglutinins when they are exposed to low ambient temperatures [23]. The deformability of the red blood cell membrane is important in the larger arteries because it allows rotation of the red cells which changes the blood into an emulsion of low apparent viscosity, but is also of critical importance at the microcirculatory level where the red blood cells must travel through capillaries with a diameter smaller than their own [22, 25]. Hence a decrease in red blood cell deformability not only increases the apparent viscosity of the blood in the larger blood vessels and, thus, augments the total resistance to flow, but also reduces the ability of those cells to ensure proper oxygenation of the tissues at the capillary level. Metabolic deprivation markedly reduces red blood cell deformability [38, 39], and it is likely that this phenomenon is a major aggravating factor in the development of peripheral vascular insufficiency [20, 40].

Achieving a normal deformability of the red blood cell membrane requires ATP and oxygen [3, 17, 38, 39]. It is likely that part of the ATP produced is used to pump Ca^{2+} out of the cell, and that an increased cellular content of the ion decreases the deformability [21, 39]. In hypoxic conditions, the augmented lactate production inhibits the glycolytic production of ATP and thus depresses the Ca^{2+} removal process. The intracellular content of Ca^{2+} rises and the red blood cell deformability decreases because the influx of Ca^{2+} from the plasma is not balanced by the pumping action of the cell membrane in the outward direction. Calcium ion influx into erythrocytes is also enhanced by catecholamines and certain prostaglandins. Hence these vasoactive substances tend to reduce red blood cell deformability even further [1]. As a consequence, the resistance to flow increases because of the augmented viscosity of the blood, and the microcirculatory supply of oxygen is reduced because of the lesser permeation of the smaller capillaries by the stiffer red blood cells. Inhibitors of Ca^{2+} influx such as cinnarizine [8] and flunarizine [7] counteract the hypoxia-induced decreases in red cell deformability.

Conclusion

When the large blood vessels supplying a part of the body are narrowed because of mechanical obstruction, vasospasm or a combination of both, despite adequate dilatation of the resistance vessels, the blood flow becomes insufficient to provide enough oxygen to the tissues when they increase their activity. As a consequence the blood becomes hypoxic, which in turn decreases the deformability of the red blood cells. This results in augmented viscosity of the blood, increased peripheral resistance and further impairment of the blood flow through the narrowed vessel. The decreased deformability, combined with the reduced blood flow favors the occurrence of 'rouleaux' formation, which also increases blood viscosity and peripheral resistance. At the microcirculatory level, the hypoxic erythrocytes cannot pass through smaller capillaries. This endangers the oxygen supply of the tissues even further. We suggest that this vicious circle can be interrupted by inhibitors of Ca^{2+} influx at two levels: (1) by antagonizing the vasospastic components of the arterial occlusion, and (2) by decreasing the Ca^{2+} content of the red blood cells (Fig. 1). This combination of effects decreases the resistance to flow through the larger vessels and allows an improved supply of blood to the tissues. The available red blood cells can fulfil their function at the microcirculatory level because they regain their normal flexibility. This interpretation explains the apparent contradiction between the observations that the resistance vessels dilate normally in patients with

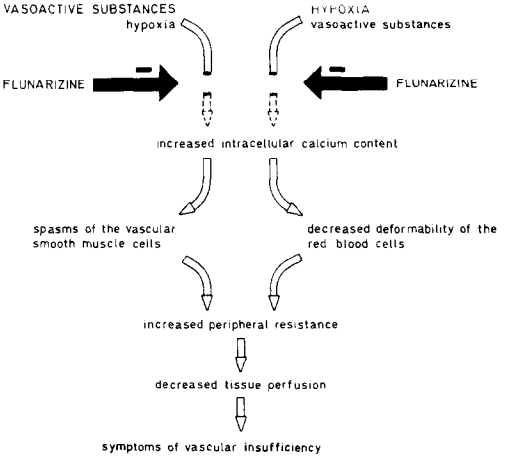

Fig. 1. Proposed dual site of action to explain why inhibitors of Ca^{2+} influx such as flunarizine improve the blood supply in peripheral vascular disease associated with vasospasm and tissue hypoxia.

peripheral vascular disease, on the one hand, and that inhibitors of Ca^{2+} influx have beneficial effects in such patients, on the other hand. Of the available inhibitors of Ca^{2+} influx, it appears that drugs such as flunarizine, which is used for the treatment of peripheral vascular diseases [37] are potentially the most interesting, since they interfere little with the normal myogenic vascular tone but inhibit spastic vasoconstrictions, and improve red blood cell deformability in hypoxic blood.

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