THE ROLE OF NITROGLYCERIN IN CARDIOVASCULAR THERAPY

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Abstract. *The use of nitroglycerin in the treatment of angina pectoris began not long after its original synthesis in 1847. Since then, the discovery of nitric oxide as a biological effector and better understanding of its roles in vasodilation, cell permeability, platelet function, inflammation, and other vascular processes have advanced our knowledge of the hemodynamic (mostly mediated through vasodilation of capacitance and conductance arteries) and nonhemodynamic effects of organic nitrate therapy, via both nitric oxide–dependent and –independent mechanisms.*

Keywords: *Nitroglycerin, inflammation, metabolism, organic nitrate, ischemic cardiomyopathy, vasorelaxation, migraine, neuroanatomical and neurochemical therapy*

Nitrates are rapidly absorbed from mucous membranes, the gastrointestinal tract, and the skin; thus, nitroglycerin is available in a number of preparations for delivery via several routes: oral tablets, sublingual tablets, buccal tablets, sublingual spray, transdermal ointment, and transdermal patch, as well as intravenous formulations. Organic nitrates are commonly used in the treatment of cardiovascular disease, but clinical data limit their use mostly to the treatment of angina. They are also used in the treatment of subsets of patients with heart failure and pulmonary hypertension. One major limitation of the use of nitrates is the development of tolerance. Although several agents have been studied for use in the prevention of nitrate tolerance, none are currently recommended owing to a paucity of supportive clinical data. Only 1 method of preventing nitrate tolerance remains widely

accepted: the use of a dosing strategy that provides an interval of no or low nitrate exposure during each 24-h period. Nitric oxide's important role in several cardiovascular disease mechanisms continues to drive research toward finding novel ways to affect both endogenous and exogenous sources of this key molecular mediator.

Nitroglycerin (NTG) patches provide potentially therapeutic NTG blood levels for 24 hours, but their effects on exercise tolerance (ExT) in patients with angina have not been well characterized. Therefore, blinded, randomized trials were performed of the acute effects of both low-dose and maximal-toler-ated-dose NTG patches and placebo on ExT in 14 patients with coronary artery disease and typical exertional angina. The bicycle exercise protocol of the National Institutes of Health was used and sublingual NTG administered as a positive control. In 7 subjects, low-dose patches produced no statistically significant effect on ExT at 4, 8 or 24 hours after administration. Comparable doses of sublingual and oral isosorbide dinitrate, NTG ointment and transmucosal NTG in previous studies have produced effects similar to those of conventional doses of sublingual NTG. Maximally tolerated doses of 2 types of NTG patches were then tested. The first (n = 8, mean NTG dose delivered 25 mg) produced increases in ExT of 82 and 72 seconds at 4 and 8 hours, respectively (both $p<0.01$), but was ineffective at 24 hours. The second patch type (n = 5, mean NTG dose delivered 22 mg) was also ineffective at 24 hours. Furthermore, even at maximal doses, peak effects on ExT were about half of those of sublingual NTG. Thus, NTG patches, even at maximal doses, appear to have smaller therapeutic effects than other long-acting nitrates and are ineffective at 24 hours. These results suggest rapid attenuation of NTG effect during prolonged maintenance of constant blood levels.

Nitroglycerin is an organic nitrate that has been used as a vasodilator in the treatment of cardiac diseases for over a century. Only recently it has been demonstrated that the vasodilator effect of this drug depends upon the formation of nitric oxide in the blood vessel wall. However, clinical and research data gathered during the last decades have suggested that nitroglycerin possesses, besides its

peripheral vasodilator effect, additional, puzzling biological activities.

This organic nitrate compound provokes reflex cardiovascular activities via its interaction with the central sympathetic system. Its cerebrovascular effect, on the other hand, is probably mediated by the local release of neuropeptides. The direct application of nitroglycerin onto brain nuclei causes a prompt increase in the neuronal discharge rate.

From a neurological point of view, nitroglycerin consistently induces a specific headache attack in patients suffering from migraine. Because of its temporal pattern and clinical characteristics, nitroglycerin-induced headache cannot be solely ascribed to the a drug-induced vasorelaxation.

The demonstration that systemic nitroglycerin administration activates a widespread set of vegetative, nociceptive and neuroendocrine structures in the central nervous system seems to further support the occurrence of central mechanisms in the biological activity of nitroglycerin.

Double labeling immunocytochemical and neuropharmacological studies have provided information on the putative neurotransmitters and neurochemical mechanisms involved in nitroglycerin-induced neuronal activation.

Introduction

A resurgence of interest in organic nitrates has been initiated by new findings that these substances can be regarded as prodrugs acting via the release of nitric oxide (NO) and by studies demonstrating that endothelium derived relaxing factor (EDRF) is chemically identical to NO (Moncada et al., 1988; Ignarro, 1989).

The growing knowledge regarding the diverse bioregulatory roles of NO in cell function and cell signaling has renewed basic scientific interest in nitrate compounds and triggered investigations on other biological actions unrelated to their well known mechanisms of vasorelaxation. Nevertheless, despite the ongoing scientific effort, many gaps still exist, especially as far as the alternative biological actions of organic nitrates are concerned.

The physiological and pharmacological actions of the various organic nitrates differ substantially. This may depends partly on their different tissue distribution,

related to their lipophilicity, and, partly on the different oxidation states of production of NO in redox chemistry.

Nitroglycerin is a highly lipophilic organic nitrate which has been considered, for years, the first-choice therapy for the treatment of angina pectoris and myocardial infarction (Chiariello et al., 1976; Murad, 1990; Murrel, 1989) (Fig. 1). The mechanism of action of nitroglycerin on the cardiovascular system is related to smooth muscle relaxation, with a consequent increase in coronary blood flow and reduction in cardiac pre- and post-loads. In the blood vessel wall, nitroglycerin acts intracellularly via the formation of NO, the active principle responsible for endothelial-controlled vasodilation (Chung and Fung, 1993; Garthwaite, 1991; Ignarro, 1991; Moncada et al., 1991). The rate of NO formation strongly correlates with the activation of soluble guanylate cyclase in vitro, resulting in the stimulation of the synthesis of cyclic-GMP (c-GMP). This latter is presumed to be the ultimate messenger responsible for nitroglycerin-induced relaxation of smooth muscle cells.

It has been known for years that headache is the most frequent side effect of nitroglycerin. Several studies have demonstrated that sublingual or intravenous (i.v.) administration of nitroglycerin to controls with no history of migraine and to migraineurs will induce a different pattern of response. Both normal subjects and migraineurs experience a dose-dependent, immediate and short-lasting headache (Dalsgaard-Nielsen, 1955; Iversen et al., 1989; Olesen et al., 1993; Sicuteri et al., 1987). However, the pain is more intense in migraineurs. More importantly, in migraine patients, this nitroglycerin-induced headache is followed by a migraine attack, delayed of one to several hours after nitroglycerin discontinuation, the intensity and characteristics of which are similar to the patient's own spontaneous attacks. The occurrence of the delayed migraine-like headache following nitroglycerin administration is considered specific and enables the diagnosis of migraine. The neurobiological background of this phenomenon has been puzzling researchers for decades. The long latency associated with the painful attacks cannot be simply ascribed to a cause exclusively targeting drug-induced vasodilatation, since the half-life of nitroglycerin in the blood compartment is in the order of 3–4

min (Murad, 1990). In addition, the delayed migraine-like headache caused by nitroglycerin is frequently associated with symptoms like nausea, photo-phobia and phono-phobia, which are attributed to the activation of structures in the central nervous system. Taken together, these findings seem to give credence to an additional, probably central, mechanism of action for nitroglycerin.

Section snippets

The bioconversion product nitric oxide

The main bioconversion product of nitroglycerin, NO, most likely plays a key role in the central mechanism of the drug. This small, membrane-permeable molecule is a critical messenger in multiple biologic pathways. First recognized as an important messenger molecule in the cardiovascular system, NO also proved to be a sui generis neuronal messenger molecule. As a neuronal signal transmitter, NO has revolutionized the classic concept of neurotransmission. NO is membrane-permeable and cannot be

Pharmacological evidence prompting a central effect for nitroglycerin

Nitroglycerin is highly lipophilic and easily crosses the blood brain barrier. The tissue distribution of nitroglycerin in the brain has only recently been described. Torfgard et al. (1989)and Torfgard and Ahnler (1991)showed that in vivo administration of nitroglycerin results in tissue drug concentration considerably higher compared to plasma, with brain concentration as high as in aorta and heart. However, aorta cGMP levels increase 15 min after systemic nitroglycerin administration, while a

Central mechanisms of the effect of nitroglycerin on the cardiovascular system

The concept that the central nervous system may play a role in the biological activities of nitroglycerin was first suggested by Kaverina et al. more than 30 years ago (Kaverina et al., 1967). While studying constrictor reflex reactions of the coronary vessels and pressor vasomotor reflexes, the authors observed that nitroglycerin had a depressing effect on these activities and that this effect was due to the action of the drug on centrally acting cardiovascular nuclei. In more detail, i.v.

Central mechanisms of the effect of nitroglycerin on the cerebrovascular system

The mechanism underlying relaxation of vascular smooth muscles induced by nitroglycerin has been studied for the most part in vitro on large peripheral vessels such as the aorta, pulmonary artery and vein. The classical view is that nitrates act directly on vascular smooth muscles to generate NO, either spontaneously or through interactions with tissue components. NO, as mentioned above, then activates soluble guanylate cyclase and thus increases cGMP and cGMP-dependent protein kinase with

Metabolic mapping of brain nuclei responding to systemic nitroglycerin administration

To document the effects of nitroglycerin on neural elements in the central nervous system we mapped Fos expression, a marker of neuronal activation (Dragunow and Faull, 1989; Morgan and Curran, 1991; Sagar et al., 1988; Sharp et al., 1989), throughout brain following subcutaneous (s.c.) injection of nitroglycerin (Tassorelli and Joseph, 1995a). In this study we show a dramatic array of Fos-immunoreactivity in a variety of nuclear complexes. Maximal expression was attained 4 hr following

Clinical implications

The clinical implications of the data presented above are quite intriguing and relate to a number of neurological disorders. First of all, the findings regarding nitroglycerin-induced neuronal activation may be regarded as a neuroanatomical and neurochemical basis for the study of migraine, especially in the light of the specific nitroglycerin-induced migraine headache described in the first paragraph of this review.

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