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Hydralazine decreases sodium nitroprusside-induced rat aortic ring relaxation and increased cGMP production by rat aortic myocytes

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Abstract

Association of hydralazine with nitrovasodilators has long been known to be beneficial in the vasodilator treatment of heart failure. We previously found that hydralazine appeared to reduce the increase in cGMP induced by sodium nitroprusside in cultured rat aortic myocytes. In order to further explore this seemingly paradoxical interaction, we extended our initial observations in rat aortic myocytes and also determined the influence of hydralazine on sodium nitroprusside-induced relaxation of rat aortic rings. Hydralazine produced a concentration-dependent inhibition of sodium nitroprusside stimulation of cGMP production and caused a rightward shift of concentration–relaxation curves in aortic rings. A possible mechanism of the hydralazine–nitroprusside interaction could be the interference with bioactivation of the nitrovasodilator to release nitric oxide. Recent evidence indicates that vascular NADH oxidase, an enzyme known to be inhibited by hydralazine, could be involved in this process. Accordingly, hydralazine was found to inhibit NADH oxidase activity in rat aortic myocytes at concentrations similar to those reducing sodium nitroprusside responses. It was concluded that antagonism of sodium nitroprusside action by hydralazine could be a consequence of interference with bioactivation of the former, apparently through inhibition of vascular NADH oxidase.

Keywords: Hydralazine; Sodium nitroprusside; Vasodilation; cGMP; NADH oxidase

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Introduction

A beneficial interaction between hydralazine and organic nitrates has been known since vasodilators began to be used in the therapy of congestive heart failure. Early clinical studies revealed an improved hemodynamic response and survival rate in patients receiving a combination of hydralazine and isosorbide dinitrate, when compared with results with either drug alone (Massie et al., 1977; Cohn et al., 1986). The superiority of this association was initially attributed to summation of the different hemodynamic actions exerted by each vasodilator on the arterial and venous portions of the circulation. Using a rat model of heart failure, Bauer and Fung (1991) found that a continuous infusion of nitroglycerin produced a beneficial reduction in left ventricular end-diastolic pressure, but that tolerance developed to this response after 8 h of infusion. Coadministration of hydralazine inhibited this phenomenon, leading the authors to conclude that prevention of tolerance could be the mechanism of the enhanced clinical efficacy of the hydralazine–nitrate combination. Clinical studies in small numbers of patients with heart failure have both confirmed (Gogia et al., 1995) and disputed (Parker et al., 1997) the beneficial effect of hydralazine in nitroglycerin tolerance.

Studies in aortic rings substantiate a hydralazine–nitroglycerin interaction at the vascular smooth muscle level, since in rat (Unger et al., 1993) and rabbit (Münzel et al., 1996) aorta, hydralazine potentiated responses to nitroglycerin in rings tolerant or not to the nitrate; negative results, however, have also been reported (Bauer and Fung, 1991). Explanations for the influence of hydralazine on nitrate tolerance include a favorable effect on renal hemodynamics (Bauer and Fung, 1991), increased availability of thiols participating in nitrate bioactivation (Unger et al., 1993), and reduction of vascular superoxide production (Münzel et al., 1996).

In a comparison recently carried out in our laboratories of the effects of hydralazine and other hydrazine derivatives on vascular tone, blood pressure and cGMP production (Vidrio et al., 2003), we found that hydralazine appeared to decrease cyclic nucleotide output by cultured rat aortic smooth muscle cells upon stimulation with sodium nitroprusside . Due to the experimental design used in that study, no statistical significance could be assigned to this finding. The possible interaction between hydralazine and sodium nitroprusside has not been studied in such detail as that between hydralazine and nitroglycerin described above. Experiments in which hydralazine and sodium nitroprusside were administered concurrently are limited to assessment of the in vitro vasorelaxant activity of sodium nitroprusside in diverse arteries from rats treated chronically with hydralazine. Either an unchanged (Nigro et al., 1989; Fuchs et al., 1996; Bennett et al., 1996) or a slightly potentiated (Shultz and Raij, 1989) sodium nitroprusside relaxation was observed. In a clinical study, sodium nitroprusside elicited similar hemodynamic responses before and during treatment with hydralazine in patients with heart failure who had developed tolerance to this vasodilator (Packer et al., 1982). Thus, our finding of what appeared to be a negative interaction between hydralazine and sodium nitroprusside on cGMP production was unexpected and of sufficient importance to deserve further characterization.

One of the hypotheses to explain the development of tolerance to organic nitrates postulates an excessive production of superoxide anion by vascular smooth muscle (Münzel et al., 1995). This leads to inactivation of the nitric oxide (NO) generated from the organic nitrate (Huie and Padmaja, 1993) and to decreased vasodilation. An important source of vascular superoxide is NADH oxidase (Cai et al., 2003), an enzyme that can be inhibited by hydralazine; it is thought that such inhibition is responsible for the tolerance-preventing effect of hydralazine (Münzel et al., 1996). On the other hand, NADH oxidase is also involved in the reduction of nitroprusside to produce NO (Mohazzab-H et al., 1999), so that