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Effect of sodium azide and sodium selenite on prostaglandin synthesis in rabbit kidney medulla slices

YOHKO FUJIMOTO*, TAKU YAMAMOTO, NOBUYUKI NIWASE, TADASHI FUJITA, *Department of Hygienic Chemistry, Osaka College of Pharmacy, Matsubara, Osaka 850, Japan*

Sodium azide, a catalase inhibitor, stimulated the generation of medullary prostaglandin E_2, while the glutathione peroxidase activator sodium selenite inhibited it. These results suggest that hydroperoxides play an important role in the control of prostaglandin synthesis.

Lipid peroxidation can modulate arachidonate turnover and prostaglandin synthesis in rabbit kidney medulla slices (Fujimoto et al 1983). Cyclooxygenase activity can be enhanced or inhibited by antioxidants depending on their type and concentration (Fujita et al 1982). On the other hand, prostaglandin cyclooxygenase activity has been shown to be inhibited by added glutathione peroxidase (Lands et al 1971; Smith & Lands 1972). The sensitivity of the cyclooxygenase to inhibition by added glutathione peroxidase has been taken as an indication of a continuous requirement for some peroxide for activation (Smith & Lands 1972; Hemler & Lands 1980). This paper deals with the effects of sodium azide and sodium selenite on the in-vitro production of prostaglandin E_2, in order to investigate the possible involvement of hydroperoxides in regulation of prostaglandin synthesis.

Materials and methods

Male rabbits (2–2·5 kg) were anaesthetized (sodium pentobarbitone, 30 mg kg^{-1}) and the kidneys were removed and rapidly chilled in ice-cold 0·9% NaCl. Slices of medulla were prepared as described by Fujimoto & Fujita (1982). In all experiments the slices (0·4 g) were preincubated in 4·0 ml of 0·15 M KCl/0·02 M Tris-HCl buffer, pH 7·4, at 4 °C for 5 min. Following preincubation, the medium was discarded, the slices rinsed twice with the Tris-HCl buffer and incubated with various concentrations of drugs at 37 °C for 30 min. After incubation, the medium was assayed for prostaglandin E_2 content by a high-pressure liquid chromatographic method (Fujimoto et al 1983). Briefly, prostaglandin E_2 extracted with ethyl acetate (approximately pH 3) was measured after its base-catalyzed conversion to prostaglandin B_2 (Jouvenaz et al 1970). Peak heights were measured for the quantification of the extracted prostaglandin B_2 relative to a prostaglandin B_2 standard prepared from authentic prostaglandin E_2.

The values are the mean ± standard error. Statistical significance was calculated using Student's paired *t*-test.

* Correspondence.

Results and discussion

Azide has been reported to inhibit the endogenous catalase activity (Morehouse et al 1983). The biochemical mechanism by which selenium acts as an antioxidant remained obscure until Rotruck et al (1973) presented some experimental evidence for the involvement of selenium in the glutathione-dependent metabolism of hydroperoxides. Those authors described an incorporation of intraperitoneally injected ^{75}Se into a protein fraction which after partial purification showed glutathione peroxidase activity. It was assumed that selenium might function as a constituent of glutathione peroxidase. To assess the potential involvement of hydroper-

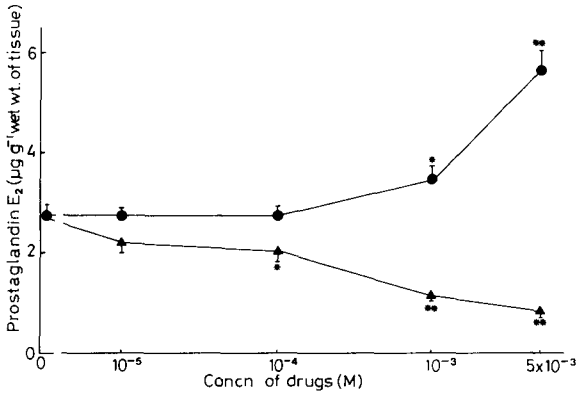

FIG. 1. Effects of sodium azide and sodium selenite on prostaglandin E_2 synthesis of rabbit kidney medulla slices. Slices were incubated for 30 min at 37 °C in 0·15 M KCl/0·02 M Tris-HCl buffer in the presence of different concentrations of sodium azide (●) or sodium selenite (▲). Each point indicates the mean of five experiments; vertical lines show s.e. $*P < 0·05$ compared to corresponding value in the absence of sodium azide or sodium selenite. $**P < 0·01$ compared with corresponding value in the absence of sodium azide or sodium selenite.

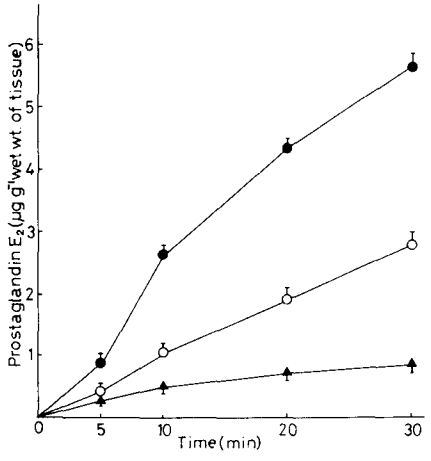

FIG. 2. Time course of prostaglandin E_2 release from rabbit kidney medulla slices. Incubations were for 30 min at 37 °C in 0·15 M KCl/0·02 M Tris-HCl buffer in the absence (○) and the presence of 5 mM sodium azide (●) or 5 mM sodium selenite (▲). Each point indicates the mean of three experiments.

oxides in regulation of prostaglandin synthesis, we have altered the concentration of hydroperoxides by inhibiting endogenous catalase activity with sodium azide, and by activating endogenous glutathione peroxidase activity with sodium selenite.

The generation of prostaglandin E_2 in medulla slices was stimulated by sodium azide, but was inhibited by the addition of sodium selenite (Fig. 1). The effects were concentration-dependent.

The effects of sodium azide or sodium selenite (5 mM) were apparent within 10 min after addition to the incubation mixture, and they persisted for 30 min (Fig. 2).

Our present data clearly showed that sodium azide, a catalase inhibitor, stimulated the synthesis of prostaglandin, and sodium selenite, an activator of glutathione peroxidase, inhibited it, indicating that hydroperoxides play an important role in the control of prostaglandin synthesis.

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