Influence of nocloprost on the vascular responses to various stimuli in the isolated perfused rabbit kidney[1]

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Received 26 March 1990; accepted 23 May 1990

Summary. Nocloprost, a new synthetic prostanoid, elicited a vasodilator action when given through the renal artery of the isolated perfused rabbit kidney. Lower concentrations of the compound inhibited the pressor response to sympathetic stimulation or to angiotensin II, but potentiated the pressor effect of exogenous noradrenaline. These results were taken as an evidence that nocloprost prevents the release of neurotransmitter by a presynaptic mechanism.
Key words. Nocloprost; rabbit kidney; angiotensin II; noradrenaline; sympathetic stimulation.

Nocloprost (NOC) is a new synthetic prostanoid which has a cytoprotective effect against gastric mucosal damage induced by various stimuli[2,3]. This compound has a potent vasodilator activity on the rabbit basilar artery[4]. No other studies concerning the cardiovascular effects of NOC have been published. Working on the tissue protective activity of NOC, we have recently observed that this compound has different effects on various vascular regions (unpublished observations). The aim of the present study was to investigate the effect of NOC on the neuroeffector junction and possible alterations in the vasoconstrictor effects of noradrenaline (NA) and angiotensin II (A II) in the resistance vessels of the isolated perfused rabbit kidney.

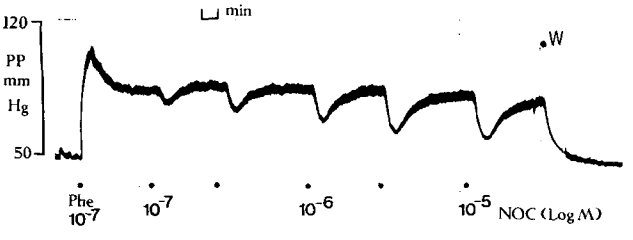
Material and methods

The experiments were carried out on isolated perfused kidneys from adult rabbits of either sex weighing 2.0–3.0 kg. The animals were anesthetized with sodium pentobarbital (35 mg/kg i.v.) and both kidneys were removed, isolated and perfused with freshly prepared warmed (37 °C) and oxygenated (5% CO_2 in O_2) Krebs solution at a flow rate of 8 ml/min, as described previously[5]. The perfusion pressure (PP) was continuously measured via a pressure transducer (Statham P 23 Dc) and recorded on a Grass polygraph (Model 79 C). A bipolar platinum electrode was placed around the renal artery and was connected to an electronic stimulator (AEL 751 B) delivering repetitive square wave pulses of 2 ms duration at 40 V. Drops of urine from the cannulated ureter were discarded.

In one series of experiments NOC was infused through the renal artery at different concentrations (10^{-8} – 10^{-5} M) and the vascular responses were measured. In the same series phenylephrine (Phe) was added to the bathing medium at a concentration of 10^{-7} M in order to produce a submaximal increase in PP. The effect of NOC was then tested again. Changes in PP due to electrical stimulation at different frequencies (5–20 Hz) were also recorded, in another series of experiments, before and after addition of NOC (10^{-8} M) to the perfusion medium. In a final series of experiments, NA and A II were infused through the cannulated artery in separate kidneys and the increases in PP were measured on the recorder before and after NOC (10^{-8} M). The increase in PP was measured on the recorder and expressed as mm Hg. The results were statistically evaluated using Student's t-test.

Results

The average initial PP of the isolated kidney was 58.0 ± 12.0 mm Hg (n = 22) after a 60-min perfusion period with Krebs solution alone. In the basal condition, infusion of NOC through the renal artery produced a slight decrease in PP, of 10.0 ± 3.0 mm Hg (n = 10) for a concentration of 10^{-6} M. Decrease in PP induced by



The effect isolated perfused rabbit kidney of nocloprost (NOC) on perfusion pressure (PP) in submaximal vasoconstriction was induced by phenylephrine (Phe). (W) indicates the elimination of Phe from perfusion medium.

The effect of nocloprost clathrate (ZK 94 726) on the pressor response induced by sympathetic stimulation, angiotensin II and noradrenaline in isolated perfused rabbit kidney (Δ mm Hg; mean ± SEM of 8 experiments)

Pressor stimuli	Control	In presence of nocloprost (10^{-8} M)
Sympathetic stimulation		
5 Hz	8.9 ± 1.2	0
10 Hz	18.4 ± 3.2	6.3 ± 1.4
20 Hz	36.5 ± 3.8	24.2 ± 4.1
Angiotensin II		
1 ng/ml	9.7 ± 2.5	2.3 ± 0.5
2 ng/ml	19.9 ± 2.1	5.6 ± 0.1
4 ng/ml	34.0 ± 3.4	8.5 ± 1.0
Noradrenaline		
5 ng/ml	13.0 ± 1.7	23.6 ± 2.6
10 ng/ml	24.7 ± 2.8	43.0 ± 1.8

NOC was not concentration-dependent under the basal condition. However, when a submaximal vasoconstriction was elicited by Phe (10^{-7} M), when the PP had reached an average value of 97.9 ± 11.0 mm Hg (n = 24), NOC produced a concentration-dependent fall in PP, followed by a longer-lasting increase (fig.). NOC at the concentration of 10^{-8} M, which did not produce a direct vascular response by itself, effectively prevented the pressor response to periarterial stimulation and A II, but significantly increased the pressor effect of NA. The results are summarized in the table.

Discussion

The results of the present study indicate that NOC has a vasodilator action on resistance vessels of the isolated perfused kidney rabbit at the concentrations used. A similar long-lasting vasodilator action of NOC has also been observed in the rabbit basilar artery[4]. However, in isolated helically cut renal artery from the same species, NOC produces a long-lasting and slowly developing contractile response (unpublished observations). This difference may be due to differences in the action of the compound on large vessels and on resistance vessels. Lower concentrations of NOC, without producing a direct vascular response, inhibited the pressor response to electrical sympathetic stimulation in the isolated perfused rabbit kidney. A similar inhibitory effect of NOC was also observed on the pressor effect of exogenous A II. In contrast, NOC potentiated the pressor effect of NA. These findings indicate that the inhibitory effect of NOC against sympathetic stimulation is probably mediated by a presynaptic mechanism which causes an inhibition of NA release from adrenergic nerve endings. The mechanism of enhancement by NOC of the contractile effect of NA in perfused kidney may be due to the potentiation of the responsiveness of the postsynaptic alpha-adrenoceptors*, or to an inhibition of the re-uptake of NA. The present findings are consistent with those of several previously published observations showing inhibitory effects of various PGs on neurotransmitter release from adrenergic nerve endings[6, 7]. The effect of NOC in preventing gastric mucosal damage due to various noxious stimuli is well known[2, 3]. Prevention of the release of an adrenergic neurotransmitter from nerve endings has been shown to be one of the mechanisms of cytoprotection by PGs[8]. The findings presented here for the kidney support this hypothesis.

1 This work was supported by a grant from the Turkish Scientific and Technical Research Council (TAG-578). Nocloprost is the gift of Dr E. Schillinger, Head of Biochemical Pharmacology, Schering AG Research Laboratories, Berlin, FRG.

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0014-4754/91/010069-02$1.50 + 0.20/0

Changes in transglutaminase activity in carbon tetrachloride-damaged rat liver

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Received 26 February 1990; accepted 20 July 1990

Summary. A significant decrease in transglutaminase (TGase) activity was observed in the cytosol and nuclear fractions of carbon tetrachloride-damaged rat liver. The degree of decrease in TGase activity in the cytosol fraction was closely related to the serum transaminase level. Gel filtration studies revealed that TGase activity in 80 kDa fractions significantly decreased, but that in 160 kDa fractions slightly increased after carbon tetrachloride treatment.
Key words. Transglutaminase; ornithine decarboxylase; serum transaminase; liver damage; carbon tetrachloride; gel filtration.

Transglutaminases (TGases, EC 2.3.2.13) are calcium-dependent enzymes that promote the formation of covalent linkages between the alkyl primary amine groups of 'amine donor' substrates and the gamma-carboxamide group of glutamine in some polypeptides that serve as 'amine acceptor' substrates. They are known to be widely distributed in various mammalian tissues both intracellularly and extracellularly[1–3]. Extracellular TGase has been shown to contribute to various biological events, including fibrin and seminal fluid clotting[1–3]. The biological function of intracellular TGase, however, has not been established, although the enzyme has been suggested to be involved in the processes of cell growth and differentiation[4, 5], and in various membrane-mediated