POTENTIATING EFFECTS OF HIGH CONCENTRATION OF SODIUM NITROPRUSSIDE ON THE CONTRACTION OF GUINEA-PIG VAS DEFERENS

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Sodium nitroprusside (Na-NP) is known to have a vasodilating action in various blood vessels (1-5). In most other smooth muscles, this drug also shows a relaxing action, though some variations in its action have been reported, but no contractile action has been presented (2, 6, 7). The relaxing action of the drug has been explained by its hyperpolarizing action (4, 5) and/or by the changes in Ca utilization (2, 8, 9). In the present studies, on the other hand, it was found that high concentrations of Na-NP potentiate the contractions induced by various agents in the guinea-pig vas deferens.

A longitudinal preparation of vasa deferentia and portal veins of the guinea-pig incubated in modified Tyrode solution (10) were used in the present experiments. A high-K Tyrode solution was made by replacing NaCl in the solution with equimolar KCl. K Tyrode solution was made by replacing all NaCl with KCl. The electrical properties were observed by the double sucrose-gap method described by Kuriyama and Tomita (11). The experimental temperature was set at 35°C.

The application of Na-NP at concentrations higher than 10^{-5} M blocked spontaneous contractions of the portal vein. Both potassium contracture and noradrenaline-induced contractions were also depressed by the drug in a concentration higher than 10^{-5} M. The heights of the phasic contraction in response to potassium and to noradrenaline at 10^{-6} M in the presence of 2×10^{-3} M Na-NP were 69±4.5% (mean±S.E., n=6) and 72±4.1% (mean±S.E., n=6), respectively, of those observed in the absence of the drug (Fig. 1). The inhibitory effects were also observed with application of the drug during the course of the potassium- or noradrenaline-induced contractions. The inhibition of the former was counteracted by increasing Ca concentrations in the incubation medium, while that of the latter was not.

In the vas deferens, on the other hand, spontaneous contractions were induced by
the application of Na-NP at a concentration higher than $5 \times 10^{-4}$ M. These contractions were not blocked by tetrodotoxin ($5 \times 10^{-7}$ g/ml) or by phentolamine ($10^{-5}$ M). Treatment of animals with reserpine (intraperitoneal injection of 3 mg/kg of reserpine 48 and 24 hr before the experiments) also showed no influence on these effects of Na-NP.

The phasic contraction of the potassium contracture was potentiated by Na-NP. The height of the phasic contraction in the presence of $2 \times 10^{-3}$ M Na-NP was $122 \pm 3.1\%$ (mean$\pm$S.E., n = 6, $P<0.0001$) of the control (Fig. 1). The tonic contraction of the potassium contracture, however, was not potentiated, but was rather suppressed by the drug. Noradrenaline- and carbachol-induced contractions were markedly potentiated by Na-NP. The contractions of the epididymal side of the vas deferens by $10^{-6}$ M noradrenaline and by $5 \times 10^{-6}$ M carbachol were composed of a rapid rising phase and a slow decreasing phase of tension. Fluctuations of tensions were observed during the course of the contractions, indicating that these contractions were tetanus-like ones induced by the burst of the spike potentials. The heights of the contractions induced by noradrenaline and by carbachol at each concentration measured in the presence of $2 \times 10^{-3}$ M Na-NP were $298 \pm 68.3\%$ (mean$\pm$S.E., n = 6) and $370 \pm 78.1\%$ (mean$\pm$S.E., n = 6), respectively, of those observed in the absence of Na-NP (Fig. 1). When Na-NP was applied during the course of noradrenaline- or carbachol-induced contraction, remarkable increase in tension was observed. These tension developments were suppressed by increasing the Ca-concentration of the incubating medium by 2 to 10 mM.

Na-NP at concentrations higher than $10^{-4}$ M caused slight depolarization of the membrane in the vas deferens (Fig. 2). The number of spikes evoked by depolarizing currents increased. In about a half of the preparations examined without applying currents, spontaneous spike discharges were initiated by this depolarization. The amplitude of electrotonic potentials induced by hyperpolarizing currents decreased in the presence of Na-NP, indicating that the membrane resistance decreased. Since it could be expected that the depolarization of the membrane would cause the potentiation of the contraction by drugs and also of the phasic contraction of the potassium contracture (12), the effects of partial depolarization by elevated K$^+$ were studied. The elevation of K$^+$ concentration to 15 or 30 mM caused a depolarization of the membrane, decrease in membrane resistance, and initiated spontaneous spike discharges. In order to match these changes with those induced by Na-NP, the K$^+$ concentration was set to 15 mM. As shown in the last three columns in Fig. 1, all of the contractions were respectively potentiated by 15 mM K$^+$ to a degree similar to that by 2 mM Na-NP.

Thus, high concentrations of Na-NP showed potentiating action on the contractions of the vas deferens induced by various agents. This potentiation might be brought about by the depolarizing action of the drug on the membrane. The effects were quite different from those on vascular smooth muscle in which the drug causes hyper-
polarization of the membrane and inhibits contractions (1–5). The suppression of NaNP-induced tension development by Ca, which was observed in the presence of noradrenaline or carbachol, may also indicate the involvement of membrane excitation in the potentiating action of the drug since Ca has been known to have a stabilizing action on membranes (13).

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References
1) Roger, F., Palmer, M.D. and Lasseter, K.C.: Sodium nitroprusside. N. Engl. J. Med. 292, 294–297 (1975)
2) Kreye, V.A.W., Baron, G.D., Lüth, J.B. and Schmidt-Gayk, H.: Mode of action of sodium nitroprusside on vascular smooth muscle. Naunyn Schmiedebergs Arch. Pharmacol. 288, 381–402 (1975)
3) Kreye, V.A.W. and Gross, F.: Nitroprusside. In Handbook of Experimental Pharmacology, Vol. 39, Antihypertensive Agents, Edited by Gross, F., p. 418–430. Springer-Verlag, Berlin, Heidelberg and New York (1977)
4) Ito, Y., Suzuki, H. and Kuriyama, H.: Effects of sodium nitroprusside on smooth muscle cells of rabbit pulmonary artery and portal vein. J. Pharmacol. Exp. Ther. 207, 1022–1031 (1978)
5) Itoh, T., Kajiwara, J., Kitamura, K. and Kuriyama, H.: Effects of vasodilator agents on smooth muscle cells of the coronary artery of the pig. Br. J. Pharmacol. 74, 455–468 (1981)
6) Katsuki, S., Arnold, W.P. and Murad, F.: Effects of sodium nitroprusside, nitroglycerin, and sodium azide on levels of cyclic nucleotides and mechanical activity of various tissue. J. Cyclic Nucleotide Res. 3, 239–247 (1977)
7) Golenhofen, K.: Theory of P and T system for calcium activation in smooth muscle. In Physiology of Smooth Muscle, Edited by Bübringer, E. and Shuba, M.F., p. 197–202. Raven Press, New York (1976)
8) Hester, R.K., Weiss, G.B. and Fry, W.J.: Differing actions of nitroprusside and D-600 on tension and 45Ca fluxes in canine renal arteries. J. Pharmacol. Exp. Ther. 208, 155–160 (1979)
9) Kuriyama, H. and Tomita, T.: The action potential in the smooth muscle of the guinea-pig taenia coli and ureter studied by the double-sucrose-gap method. J. Gen. Physiol. 65, 147–162 (1976)
10) Shimodan, M. and Sunano, S.: The initiation of phasic and tonic contraction by potassium and the effect of calcium, multivalent cations and Ca-antagonist on potassium contraction in guinea-pig vas deferens. Japan. J. Physiol. 31, 15–27 (1981)
11) Kuriyama, H. and Tomita, T.: The action potential in the smooth muscle of the guinea-pig taenia coli and ureter studied by the double-sucrose-gap method. J. Gen. Physiol. 55, 147–162 (1976)
12) Urquilla, P.R., Westfall, D.P., Goto, K. and Fleming, W.W.: The effects of ouabain and alteration in potassium concentration on the sensitivity to drugs and membrane potential of the smooth muscle of the guinea-pig and rat vas deferens. J. Pharmacol. Exp. Ther. 207, 347–355 (1978)
13) Tomita, T.: Electrical properties of mammalian smooth muscle. In Smooth Muscle, Edited by Bübringer, E., Bradin, A., Jones, A. and Tomita, T., p. 197–243. Edward Arnold, London (1979)