istration, especially since it penetrates blood vessel walls non-uniformily (Török & Bevan 1971). Another factor contributing to the greater efficacy of intraluminal noradrenaline, could be non-uniformity of α-adrenoceptors in the vascular muscle which enables NA to pass from the intima to the receptors more easily.

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Effect of cocaine on noradrenaline contractions of mesenteric vein: pre- or postjunctional mechanism?

P. C. O'Connor*, P. Slater, *Department of Physiology, University of Manchester, Manchester M13 9PT, U.K.*

Cocaine potentiates noradrenaline (NA) in tissues with a sympathetic innervation by inhibiting neuronal uptake (Macmillan 1959; Iversen 1967). However, a second, postjunctional, mechanism for this potentiation has been demonstrated (Kalsner & Nickerson 1969a; Kalsner 1974). It has been shown, with the spleen, trachea, nictitating membrane, rabbit ear artery and aorta, that the role of pre- and postjunctional mechanisms in relation to the potentiation of noradrenaline by cocaine is not uniform (Hertting et al 1961; de la Lande & Waterson 1967; Foster 1967, 1969; Reiffenstein 1968; Kalsner & Nickerson 1969b; Levin & Furchgott 1970; Draskoczy & Trendelenburg 1970; Innes & Karr 1971; Granata & Langer 1973; Kalsner 1974). Although the relative importance of the two mechanisms also varies among different vascular beds (Varma & McCullough 1969; Davidson & Innes 1970; Innes & Karr 1971; Granata & Langer 1973), very little is known about the potentiation of NA by cocaine in individual vessels, particularly veins.

* Correspondence: Department of Medicine, The Royal Infirmary, Glasgow, Scotland.

We have examined the effect of cocaine on the contractions produced by NA in the guinea-pig isolated portal mesenteric vein. Prejunctional uptake of NA in relation to cocaine was determined by pretreating guinea-pigs with 6-hydroxydopamine (6-OHDA) to produce a sympathetic chemical denervation of the tissue (Thoenen & Tranzer 1968).

Normal (control) and 6-OHDA pretreated guinea-pigs (300–500 g) of either sex were used. 6-OHDA hydrochloride was administered under ether anaesthesia. A femoral vein was exposed and 6-OHDA (250 mg kg^{-1}), freshly dissolved in 0·9% NaCl containing 0·2 mg kg^{-1} of ascorbic acid, was administered intravenously. The incision was infiltrated with a local anaesthetic and sutured. The animals were killed after 24 h, and a ligature was tied round the portal vein close to the liver and the vein traced to the duodenum, which was transected and retracted. A second ligature was applied and 2–2·5 cm of portal and anterior mesenteric vein was isolated. The vein was mounted in a tissue bath containing oxygenated Tyrode solution at 37 °C. One end of the vein was secured and the free end was attached to a calibrated, isometric transducer to record longi-

tudinal tension, changes in which represent the contractions of the longitudinal muscle layer. The output from the transducer was amplified and displayed on a pen recorder. The preparation at a tension of 1 g, was allowed to equilibrate for 1 h in Tyrode solution, which was replaced every 10 min.

Contractions of the smooth muscle were recorded following the addition of cumulative doses of NA, freshly prepared in Tyrode solution. Cocaine (3×10^{-5} M) was added to the bath fluid and remained in contact with the tissue for 30 min before the addition of NA. Vein preparations were subjected to electrical field stimulation, using 1 ms duration pulses applied via ring electrodes, while changes in longitudinal tension were recorded. Portal mesenteric veins from normal guinea-pigs produced voltage- and frequency-dependent contractions when stimulated with electrical pulses. In contrast, 9 veins removed from animals pretreated with 6-OHDA failed to respond to electrical stimulation with 1 ms pulses, therefore most of the sympathetic innervation had been destroyed.

18 isolated veins, from 9 control and 9 6-OHDA pretreated guinea-pigs, were exposed to a supramaximal concentration (10^{-4} M) of NA, before and after 30 min exposure to cocaine (3×10^{-5} M). The maximum longitudinal tension generated by the normal preparations (7·8 ± 0·8 g mean ± s.e.) was the same as that produced by the denervated veins (8·1 ± 0·8 g) and was not affected by cocaine. In the presence of cocaine, the maximum contraction produced by NA (10^{-4} M) was 8·1 ± 0·8 g in normal veins and 7·7 ± 0·8 g in denervated veins. All contractions are expressed as a percentage of the maximum response.

Cumulative doses of noradrenaline were added to 9 veins from normal guinea-pigs and 9 from 6-OHDA treated animals to produce final bath concentrations of 10^{-7} to 10^{-4} M. Each vein was then treated with cocaine (3×10^{-5} M) for 30 min and the contractions produced by noradrenaline were repeated. The mean dose-response curves are shown in Fig. 1. Cocaine significantly potentiated NA in normal vein preparations, and the mean dose-response curve was shifted to the left (Fig. 1A). In the absence of cocaine, the mean dose-response curve for NA on 6-OHDA treated veins was to the left of the comparable curve from normal veins (Fig. 1A, B). Increased sensitivity of the veins to NA after 6-OHDA denervation is a well known response (de Champlain et al 1975). In contrast to normal veins, cocaine had no effect on the mean dose-response curve for NA obtained with the denervated veins (Fig. 1B). A quantitative measure of the cocaine potentiation was obtained by calculating the log-dose ratio (Foster 1967) for each experiment (Table 1). Cocaine potentiated NA in normal veins but had no effect in 6-OHDA-treated veins.

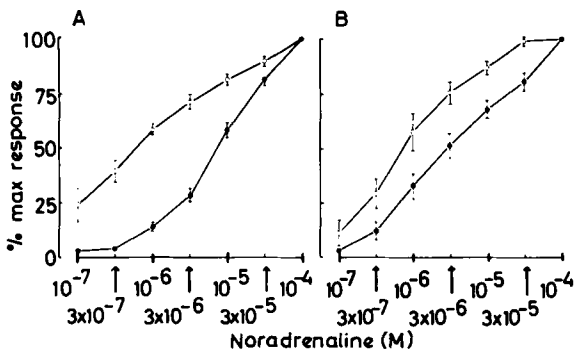

FIG. 1. The mean responses of the longitudinal muscle to cumulative doses of NA (●——●) or NA plus 3×10^{-5} M cocaine (○——○) to 9 portal mesenteric veins from A: normal and B: 6-OHDA pretreated guinea pigs. Vertical bars represent s.e. mean. Comparisons of cocaine treated with normal using a *t*-test: $^{*}P < 0.01$.

The ability of cocaine to potentiate catecholamines in isolated tissues results mainly from inhibition of the amine uptake mechanism in sympathetic nerve terminals (Furchgott et al 1963) is termed $Uptake_1$ and is the main process terminating the action of NA (Iversen 1967). Kalsner (1974) has proposed that cocaine has another mechanism for potentiating catecholamines, a post-junctional action beyond the noradrenaline receptor site. It is established that cocaine inhibits the uptake mechanism now called $Uptake_1$ in vascular smooth muscle (Whitby et al 1960; Maxwell et al 1968; Rolewicz et al 1970; Greenberg & Long 1974). However, there have been reports that cocaine potentiates NA in circumstances where $Uptake_1$ is ineffective. For example, cold storage of rabbit aortic strips, a procedure that substantially impairs catecholamine uptake, had no effect on the potentiation by cocaine (Varma & McCullough 1969; Kalsner & Nickerson 1969b). Furthermore, although cocaine potentiated both NA and isoprenaline in isolated strips of spleen, it only inhibited the neuronal uptake of NA (Davidson & Innes 1970). Cocaine also potentiated methoxamine in rabbit aortic strips (Kalsner & Nickerson 1969b), despite the fact that methoxamine is taken up by nerve terminals only to a negligible extent (Trendelenberg et al 1970).

Table 1. Cocaine potentiation of NA expressed as the log-dose ratio (Foster 1967) in portal mesenteric vein preparations.

Log-dose ratios	
Normal veins	6-OHDA veins
1·79	0·04
1·28	0·09
1·30	0
1·88	0·25
1·75	0·02

The responses of the veins to NA (50% of maximum) were potentiated by cocaine (3×10^{-5} M).

Sympathetic denervation provides the most critical test of the importance of $Uptake_1$. Where the action of cocaine is solely due to inhibition of NA uptake by nerve terminals, the effect will be lost when the neurons are destroyed. In contrast to the present findings, cocaine potentiated NA in surgically denervated rat portal veins (Johansson et al 1970). The present findings show that veins removed from 6-OHDA-treated guinea-pigs also failed to respond to electrically-induced neuronal stimulation, and more importantly, the 6-OHDA treatment abolished the potentiation by cocaine of the noradrenaline contractions, without affecting the maximum NA response. There is therefore little doubt that the potentiation of NA by cocaine in the portal mesenteric vein is due entirely to inhibition of neuronal uptake, in contrast with the aorta, in which uptake inhibition by cocaine is of minor importance (Kalsner & Nickerson 1969b). These discrepancies might reflect differences in the density of adrenergic innervation of the vascular smooth muscle or in the direct myogenic effects of cocaine, thus, in portal mesenteric veins, the local anaesthetic property of cocaine could reduce myogenic activity and offset the neuronal potentiation. However, because cocaine altered neither the shape of the dose-response curve nor the maximum contraction, it is unlikely that it depressed the smooth muscle. These findings, which demonstrate that results obtained by adding cocaine to one vascular tissue cannot be extrapolated to all arteries and veins, help to emphasize that vascular smooth muscle has significantly different properties depending on its anatomical location (Bevan 1979).

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