Comparison of the Effect of Naloxone on Cerebral Versus Mesenteric Arterial Smooth Muscle in Feline and Primate Species

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SUMMARY This study was conducted in order to investigate naloxone's in vitro action on both epinephrine-induced constriction of mesenteric artery and norepinephrine-induced constriction of cerebral arteries in different species (cat and monkey). Naloxone (3 × 10⁻⁵M) augmented the epinephrine-induced constriction of both feline and monkey mesenteric artery at epinephrine concentrations of 10⁻⁷ to 10⁻⁵M. Naloxone (3 × 10⁻⁵M) suppressed the constriction of feline basilar artery induced by high concentrations (10⁻⁴, 10⁻³ and 3 × 10⁻⁴M) of norepinephrine, while it failed to alter the constriction induced by lower concentrations (10⁻⁷ to 10⁻⁵M) of norepinephrine. The constrictor response of monkey basilar artery to norepinephrine (10⁻⁴ to 10⁻⁵M) was not altered by treatment with naloxone (3 × 10⁻⁴ and 3 × 10⁻⁵M).

Such varying effects of naloxone in different tissues and species may have to be taken into account when evaluating the cerebral blood flow changes following naloxone administration.

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presentation, the control values were averaged together. When \( p \) was smaller than 0.05, values were considered to be significantly different. Computation of dose-response curves and \( E_{D_{50}} \) values was done using probit analysis with the SAS (Statistical Analysis System) computer program. Drugs and solutions used in this study were \((-\)epinephrine\(+\)) bitartrate (Sigma Chemical Co.), \((\pm)-\)arterenol hydrochloride (Sigma Chemical Co.) and naloxone (Endo Laboratories, Inc. lot 82-037). Norepinephrine or epinephrine was dissolved using 50 mM phosphate buffer solution (pH 7.4). Naloxone was dissolved in saline.

Results
Effects of Naloxone on Norepinephrine-induced Constriction of Basilar Artery

The constrictor responses of feline basilar artery to low concentrations (<10^{-5}M) of norepinephrine was poor, but it responded fairly well to higher concentrations (10^{-4}, 10^{-3} and 3 \times 10^{-3}M) of norepinephrine. Naloxone at concentration of 3 \times 10^{-5}M suppressed the contraction of feline basilar artery induced by high concentrations (10^{-4}, 10^{-3} and 3 \times 10^{-3}M) of norepinephrine while it failed to alter the contraction induced by lower concentrations (10^{-7}, 10^{-6} and 10^{-5}M) of norepinephrine (fig. 1). Fifteen minutes after changing nutrient Kreb's solution in the bath norepinephrine dose-response curve returned to original control values.

Monkey basilar artery responded well to norepinephrine. The \( E_{D_{50}} \) value (95% confidence interval) of norepinephrine was 1.00 (0.7-1.6) \times 10^{-7}M. As shown in figure 2, naloxone at concentrations of 3 \times 10^{-6}M and 3 \times 10^{-5}M did not show any effect on the norepinephrine-induced constriction of monkey basilar artery at each norepinephrine concentration tested (10^{-8} to 10^{-5}M).

Effects of Naloxone on Epinephrine-Induced Constriction of Mesenteric Artery

The constrictor responses of mesenteric artery to epinephrine were almost equal between cat and monkey. The \( E_{D_{50}} \) values (95% confidence interval) of epinephrine in cat and monkey were 1.76 (0.85-3.67) \times 10^{-6}M and 2.32 (1.23-4.45) \times 10^{-6}M, respectively.

Naloxone at 3 \times 10^{-5}M augmented the epinephrine-induced constriction of feline mesenteric artery at epinephrine concentrations of 10^{-7}, 3 \times 10^{-7}, 10^{-6} and 3 \times 10^{-6}M (fig. 3). The epinephrine-induced constriction of monkey mesenteric artery was also augmented by 3 \times 10^{-5}M naloxone at epinephrine concentrations of 10^{-7} to 10^{-6}M (fig. 4). The constrictor responses of both feline and monkey mesenteric artery to high concentrations of epinephrine, however, were not altered by the treatment with 3 \times 10^{-5}M naloxone. The epinephrine dose-response curve returned to control values fifteen minutes after changing the nutrient Kreb's solution in the bath.

Discussion

The present results demonstrated that naloxone (3 \times 10^{-5}M) suppressed the constrictor responses of feline basilar artery to high concentrations (10^{-4}, 10^{-3} and 3 \times 10^{-3}M) of norepinephrine, while it failed to alter the responses to lower concentrations of norepinephrine. These findings may indicate the norepinephrine dose-response curve in the feline basilar artery could be resolved into two components: naloxone sen-
VASCULAR EFFECTS OF NALOXONE/Sasaki et al

These findings indicate that naloxone exerts differing effects on norepinephrine-induced constriction of cerebral artery among species. Such varying effects of naloxone on the norepinephrine-induced constriction of cerebral artery may have to be taken into account in some species when evaluating the changes of CBF following naloxone administration. In dogs and monkeys, naloxone’s action on norepinephrine-induced constriction of cerebral artery appears to be compatible with CBF changes following naloxone administration. In dogs, where naloxone showed a vasodilating effect on the norepinephrine-induced constriction of cerebral artery, it has been reported that CBF was increased by naloxone administration without corresponding changes in cerebral metabolism. In monkeys, where naloxone failed to alter the constrictor responses of cerebral artery to norepinephrine, CBF was not changed by naloxone administration.

In cats, however, naloxone’s action on norepinephrine-induced constriction of the cerebral artery does not appear to be consistent with the CBF changes following naloxone administration. The present results demonstrated naloxone’s vasodilating effect on norepinephrine-induced constriction of feline cerebral artery in vitro, while it has been reported by Grandison, et al that CBF and brain metabolism were decreased by naloxone. Therefore, the vasodilating effect of naloxone on the norepinephrine-induced constriction in vitro seems to contradict the CBF changes in cats following naloxone administration. The reduction of CBF

**Figure 3.** Epinephrine dose-response curves in feline mesenteric arteries with and without naloxone (3 x 10^{-5}M) treatment. Results are expressed as means ± SEM. * = p < 0.05. n = number of specimens tested.

sitive (high concentrations of norepinephrine) and naloxone insensitive (low concentrations of norepinephrine). This hypothesis seems to be compatible with the suggestion by Edvinsson and Owman that the norepinephrine-induced constriction of feline cerebral artery is in part mediated through an unusual type of α-adrenoceptor in the arteries. A two component dose-response curve of norepinephrine has also been noted in the rabbit cerebral artery. Duckles and Bevan have suggested that the constrictor response of rabbit cerebral artery to high concentrations of norepinephrine is mediated through receptors other than the typical α-adrenoceptors.

The mechanism of the vasodilating effects of naloxone on the constrictor responses to high concentrations of norepinephrine is unknown, though we have previously demonstrated that the vasodilating effect of naloxone on norepinephrine-induced constriction of canine basilar artery does not result from antagonistic action on opiate receptors, or from direct inhibition of α-adrenoceptors, or direct stimulation of β-adrenoceptors in cerebral arterial smooth muscle. Further studies will be necessary in order to investigate the precise mechanism of this vasodilating effect of naloxone.

The present results also demonstrated that the constrictor responses of monkey basilar artery to norepinephrine were not altered by the naloxone treatment.

**Figure 4.** Epinephrine dose-response curves in monkey mesenteric arteries with and without naloxone (3 x 10^{-5}M) treatment. Results are expressed as means ± SEM. * = p < 0.05. n = number of specimens tested.
may be due to a reduction in brain metabolism which results in cerebral vasoconstriction through the metabolic component of autoregulation overriding the vasodilation caused by naloxone.

The effects of naloxone on epinephrine or norepinephrine-induced contraction were quite different when comparing the cerebral artery to the mesenteric artery. Naloxone (3 × 10⁻⁵) augmented the constrictor responses of either feline or monkey mesenteric artery to low concentrations of epinephrine. It has also been demonstrated that naloxone (3 × 10⁻⁷ to 3 × 10⁻⁶) selectively augmented the epinephrine or norepinephrine-induced constriction of canine mesenteric artery (unpublished data, Sasaki, et al). Therefore, there seems to be no species differences in naloxone’s augmenting effects on epinephrine-induced constriction of mesenteric artery. Those augmenting effects may, in part, participate in the improvement of systemic circulation following naloxone administration. Our recent work (unpublished, Sasaki, et al) has suggested that this augmenting effect of naloxone on the epinephrine-induced constriction results from inhibition of extraneuronal uptake of catecholamines since the augmentation of norepinephrine-induced constriction of canine mesenteric artery by naloxone was inhibited by the pre-treatment of the specimens with normetanephrine.

In summary, the present results revealed the varying effects of naloxone on epinephrine or norepinephrine-induced constriction of arterial specimens in different tissues and species. Such varying effects of naloxone may have to be taken into account in some species when evaluating the changes of CBF following naloxone administration.

References

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