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EFFECTS OF 5-HYDROXYTRYPTOPHOL, A 5-HYDROXYTRYPTAMINE METABOLITE, ON ISOLATED CEREBRAL ARTERIES OF THE DOG

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5-Hydroxytryptophol (5-HTOL) caused a dose-dependent contraction of helically-cut strips of dog cerebral arteries. The 5-HTOL-induced contraction was suppressed by cinanserin, as was the contraction induced by 5-hydroxytryptamine (5-HT). Treatment with 5-HTOL shifted the dose-response curve for 5-HT to the right and downward in a dose-dependent manner, but did not attenuate the contractile response to prostaglandin $F_{2\alpha}$. It may be concluded that 5-HTOL elicits cerebroarterial contractions by activating tryptaminergic receptors and also interferes with the action of 5-HT on the receptors.

Introduction 5-Hydroxytryptamine (5-HT) is a potent cerebroarterial constrictor (Toda & Fujita, 1973), and is converted by monoamine oxidase to 5-hydroxyindoleacetaldehyde, which is degraded by aldehyde dehydrogenase to 5-hydroxyindoleacetic acid (5-HIAA) or by aldehyde reductase to 5-hydroxytryptophol (5-HTOL). 5-HIAA relaxes isolated cerebral arteries and does not interfere with the contractile response to 5-HT (Toda, Hojo, Sakae & Usui, 1974). On the other hand, 5-HTOL appears to possess 5-HT-like vasoconstrictor activity (Allen, Gross, Henderson & Chou, 1976); however, the mechanism of contraction and the interaction between this metabolite and 5-HT have not been determined. The present study was undertaken to analyze the effect of 5-HTOL on dog isolated cerebral arteries and to clarify its interaction with 5-HT.

Methods Cerebral arteries (basilar and middle cerebral) were isolated from mongrel dogs of either sex, which had been anaesthetized with sodium pentobarbitone (50 mg/kg, i.p.) and killed by bleeding from common carotid arteries. The arteries were cut into helical strips and fixed under a resting tension of 1.5 g in a muscle bath containing modified Tyrode solution (Toda, Hayashi & Hattori, 1978). The upper end of the strip was connected to a force-displacement transducer (Nihonkoden Kogyo Co., Tokyo). The bathing media were maintained at 37 ± 0.5°C and aerated with a mixture of 95% O_2 and 5% CO_2. 5-HT and 5-HTOL were added directly to the bathing media in cumulative concentrations. Maximum contractions induced by 5-HT in normal solutions were taken as 100%, and contractions induced by 5-HTOL or 5-HT in the presence of 5-HTOL are expressed in relation to this.

Results

In cerebral arterial strips, the addition of 5-HT in concentrations ranging from 10^{-9} to 2×10^{-6} M caused a dose-dependent contraction. Further increase in concentrations of 5-HT caused relaxations. 5-HTOL (2×10^{-6} to 2×10^{-4} M) also produced contractions in a dose-dependent manner (Figure 1a). The maximum contraction induced by 2×10^{-4} M 5-HTOL was 52 ± 6% of the contraction induced by 2×10^{-6} M 5-HT. The potency of 5-HTOL for inducing contractions was approximately 1/2000 that of 5-HT. When preparations were repeatedly washed with fresh solution and equilibrated for 40 to 50 min, the responses were reproducible. Treatment for 20 min with 10^{-6} M cinanserin suppressed the contractions induced by both 5-HTOL and 5-HT.

Treatment for 20 min with 10^{-5} M 5-HTOL did not significantly alter the contractile response to 5-HT; however, further increase in the concentrations to 5×10^{-5} and 2×10^{-4} M shifted the dose-response curve for 5-HT to the right and downward in a dose-dependent manner (Figure 1b). After repeated washing, the inhibition was reversed. Treatment with 5-HTOL (2×10^{-4} M) failed to attenuate the contractile response to prostaglandin $F_{2\alpha}$ (2×10^{-8} to 10^{-5} M) in all 3 cerebral arteries in which it was tested.

Discussion The addition of 5-HTOL caused a dose-related contraction of isolated cerebral arteries of the dog which was suppressed by cinanserin in a concentration sufficient to antagonize significantly the response to 5-HT. These findings suggest that the contractile response to 5-HTOL is due to activation of tryptaminergic receptors.

Treatment with 5-HTOL attenuated the contractile response to 5-HT in a dose-dependent manner but did not reduce the response to prostaglandin $F_{2\alpha}$. It appears that 5-HTOL specifically antagonizes 5-HT

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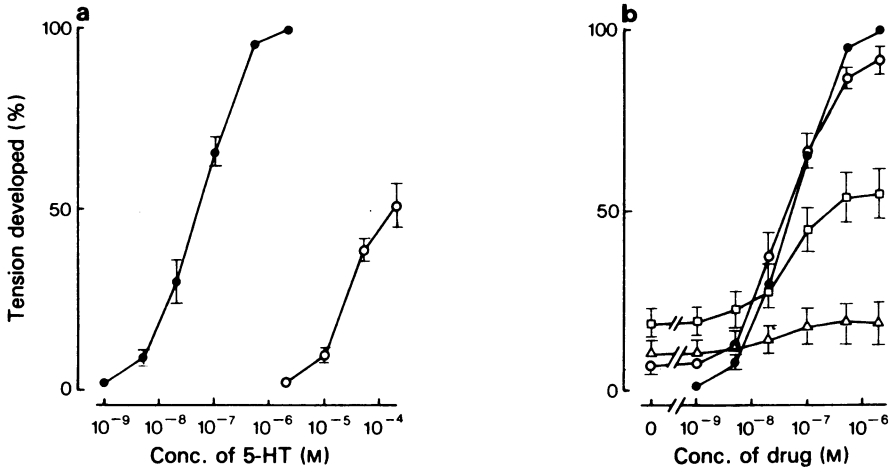

Figure 1 Dose-response curves for 5-hydroxytryptophol (5-HTOL) and 5-hydroxytryptamine (5-HT) in cerebral arterial strips. (a) Contractions induced by 2×10^{-6} M 5-HT (●) were taken as 100%; the absolute value of the maximal contractions averaged 1996 ± 368 mg ($n = 9$); (○) 5-HTOL ($n = 9$). (b) Contractions of cerebral arteries induced by 2×10^{-6} M 5-HT (●) in control media were taken as 100%; the absolute value averaged 2214 ± 512 mg ($n = 9$). Values at 'zero' on the abscissa represent contractions induced by 5-HTOL alone; during a 20 min incubation period, the arterial tone was stabilized at the level shown. (○) 5-HTOL 10^{-5} M ($n = 6$); (□) 5-HTOL 5×10^{-5} M ($n = 6$); (△) 5-HTOL 2×10^{-4} M ($n = 8$). Vertical bars represent s.e. means.

actions on cerebroarterial strips as do methysergide, lysergic acid diethylamide, ergotamine and cyproheptadine (Toda, Hayashi, Fu & Nagasaka, 1976; Müller-Schweinitzer, 1976; Edvinsson, Hardebo & Owman, 1978). 5-Hydroxykynurenamine, a metabolite of 5-HT via a different degradation pathway (Hirata & Hayaishi, 1972), possesses a similar 5-HT-like action on cerebroarterial smooth muscle and an antagonistic action against 5-HT (Toda, Tokuyama, Senoh, Hirata & Hayaishi, 1974), while 5-HIAA, a major metabolite of 5-HT, fails to induce such actions (Toda, Hojo, Sakae & Usui, 1974). It may be concluded that a hydroxy group or an amino group, but not a carboxyl group, at the end of the long side chain of 5-HT metabolites is related to the agonistic and antagonistic actions.

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