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PRESSOR EFFECTS OF TRYPTAMINE ANALOGUES

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1 Methylation of tryptamine in the 1-position had little effect on the potency of the drug as a pressor agent in the intact anaesthetized rat.

2 In contrast, substitution of a benzo[b]thiophene ring system for the indole ring decreased the pressor activity.

3 Pretreatment of the animals with reserpine reduced the pressor effect of tryptamine and its benzo[b]thiophene analogue while increasing the effect of the 1-methylindole analogue.

4 Pretreatment with phenoxybenzamine reduced the pressor effect of all three compounds.

Introduction

Since the effects of tryptamine on guinea-pig isolated ileum were not inhibited by atropine or antihistamines, and, since a strip desensitized by tryptamine was insensitive to 5-hydroxytryptamine and vice versa, Gaddum (1953) concluded there must be a specific tryptamine receptor. Rocha e Silva, Valle & Picarelli (1953) defined a 5-hydroxytryptamine receptor in guinea-pig ileum differing from those for acetylcholine, bradykinin, histamine, nicotine and pilocarpine. Gaddum & Hameed (1954) reported similar receptors in rat uterus and in the vasculature of the rabbit isolated ear. Gaddum & Picarelli (1957) defined two types of tryptamine receptor in the guinea-pig ileum, one blocked by morphine and the other by phenoxybenzamine.

The effect of tryptamine on blood pressure was first noted by Laidlaw (1912). The effects of tryptamine as a pressor substance have been compared to those of 5-hydroxytryptamine by Reid (1951), Reid & Rand (1951) and Page (1952) and ourselves (Hixson, Bosin, Zabik & Maickel, 1973). More recently, Winter, Gessner & Godse (1967) examined the effects of a series of amines on the rat isolated fundus preparation, and found that tryptamine and its benzo[b]thiophene analogue had higher relative intrinsic activities but lower affinities than 5-hydroxytryptamine.

Methods

Adult, male Sprague-Dawley rats (300–350 g) were obtained from Murphy Breeding Laboratories, Plainfield, Indiana, U.S.A. and maintained on Purina Lab Chow and tap water *ad lib* for 7–10 days before experimental use. Pentobarbitone sodium (Nembutal), reserpine (Serpasil), heparin, and tryptamine hydrochloride were purchased from commercial sources. Phenoxybenzamine hydrochloride (Dibenzyline) was kindly supplied by Smith-Kline and French Laboratories. 3-(2-Aminoethyl)benzo[b]thiophene (tryptamine-S), and 1-methyl-3-(2-aminoethyl)-indole (tryptamine-1-Me) were synthesized and supplied by Dr E. Campaigne, Department of Chemistry, Indiana University.

Surgical procedure

Animals were anaesthetized with pentobarbitone, intraperitoneally as follows: controls—60 mg/kg; reserpine pretreated—50 mg/kg; phenoxybenzamine pretreated—45 mg/kg. When pinching the tail elicited no response, the rats were placed on their backs on a small animal operating board (Interex Corp.). The trachea was cannulated to insure a free airway and the common carotid artery was ligated at the superior end then clamped at the inferior end. A cannula of PE 50 tubing was inserted into the artery through a small incision, attached to a 23 gauge needle, and connected via a three-way stopcock to a Statham strain gauge model P23AA and to the pressure bottle of a mercury manometer system. The system was filled with 0.93% w/v NaCl solution containing heparin 1000 u/ml. The strain gauge was connected to the coupler of an Offner Type RB Dynograph (Beckman Instrument, Inc.), or, via a Bridge Preamplifier (Narco Biosystems, Inc.) to a Physiograph model PMP-4A (Narco Biosystems, Inc.). The system was flushed briefly with the heparin/saline solution, and blood pressure recorded to confirm the intact system.

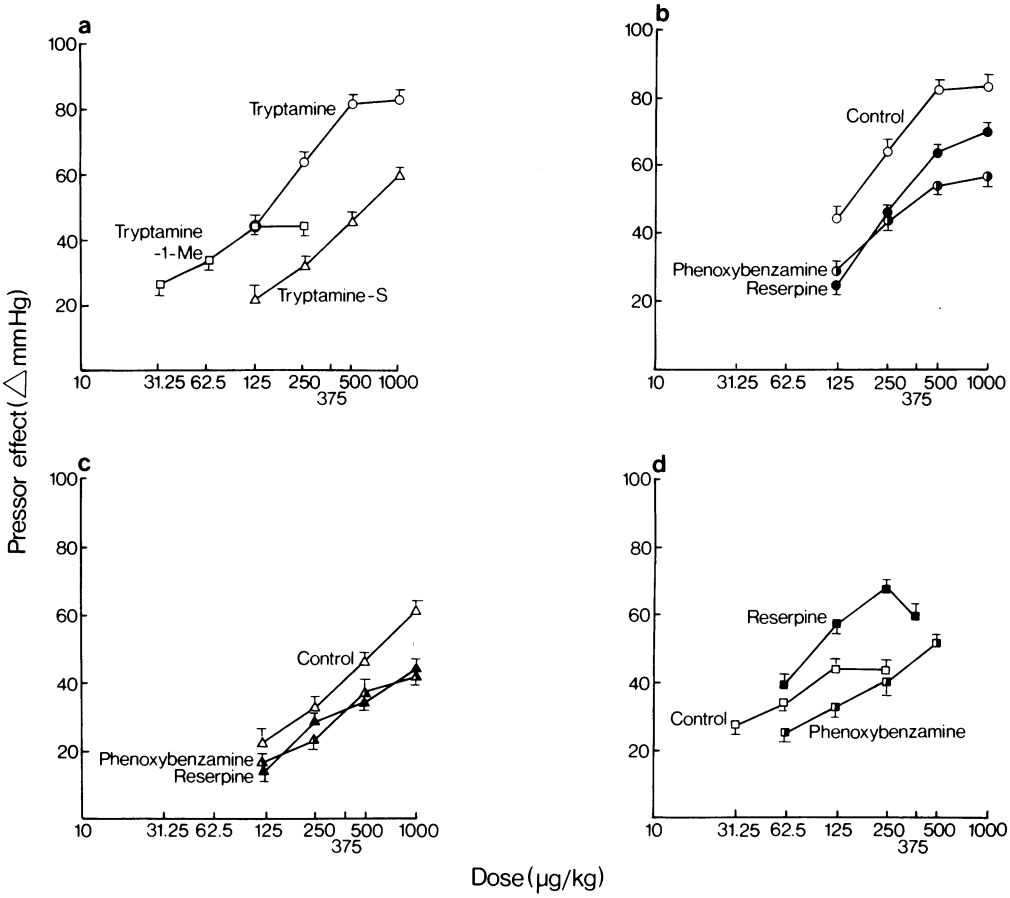

Figure 1 Pressor effects of tryptamine and analogues. Baseline blood pressure values were 110 ± 5 mmHg in control rats, 60 ± 4 mmHg in reserpine-pretreated rats, and 86 ± 5 mmHg in phenoxybenzamine-pretreated rats. (a) Effects of tryptamine and analogues in control rats; (b) effects of pretreatments on pressor responses to tryptamine; (c) tryptamine-S, and (d) tryptamine-1-Me. Vertical bars indicate s.e. mean.

The external jugular vein was then exposed for a distance of 1 to 1.5 cm. A cannula of PE 50 tubing was inserted, attached to a 23 gauge needle and connected via a three-way stopcock to a 3 ml syringe containing a flushing solution of the heparin/saline solution used above, and a 1 ml syringe containing the test drug.

Testing method

Test drugs were made up in the heparin/saline solution such that a volume of 0.1 ml contained a specific dose of the drug. Each of four animals was given four doses of drug four times, in a Latin square design, over a period of 1–2 hours. In addition, a Latin square was designed based on the sequence of the four cycles, so that each animal received a different sequence of cycles. Reserpine (10 mg/kg i.p.) was given 22–26 h before testing. Phenoxybenzamine (5 mg/kg i.p.) was given 1.5 h before testing.

Results

In control animals tryptamine caused a significant pressor response over a range of 125–1000 μg/kg. Both of the analogues also showed a pressor effect; tryptamine-S was less potent than tryptamine, while tryptamine-1-Me had a similar potency to tryptamine (Figure 1a). Transitory respiratory paralysis was seen occasionally after 500 μg/kg and usually after 1000 μg/kg of tryptamine and tryptamine-S. Tryptamine-1-Me was more toxic; 1000 and

500 μg/kg invariably caused a fatal cessation of respiration.

Pretreatment of rats with a single dose of reserpine reduced the pressor effects of typtamine and trypamine-S significantly (Figures 1b, c). Respiratory paralysis of brief duration occurred after the higher doses with both tryptamine and tryptamine-S. In contrast, the pressor responses to the doses of tryptamine-1-Me given to reserpine-treated animals, 62.5, 125 and 250 μg/kg, were greater in the same doses than in normal animals (Figure 1c).

In animals pretreated with phenoxybenzamine, the pressor effects of all three compounds were significantly reduced when compared to their actions in control animals (Figures 1b, c, d). Of particular interest is the fact that respiratory paralysis due to the pressor agents was a rare occurrence after phenoxybenzamine pretreatment.

Discussion

The scientific literature contains a variety of references to the existence of tryptamine receptors (Erspamer, 1954). However, it is difficult to extrapolate from responses of isolated preparations to those of the vasculature in the intact animal. While tryptamine may interact with its own specific peripheral receptor(s) to increase blood pressure, one cannot rule out the possibility of a centrally-mediated component.

Since the dose-response curves were not parallel the relative potencies of the analogues depended to some extent on the dose. Tryptamine-S was less potent than the other two compounds. Both pretreatments (reserpine and phenoxybenzamine) reduced the pressor effects of tryptamine and tryptamine-S. In contrast, reserpine pretreatment increased the pressor response to tryptamine-1-Me, while phenoxybenzamine caused a decrease in the pressor activity of this analogue. These results argue against the three agonists acting on a single receptor.

Chiu, Harrison, Maickel & Bosin (1973) have reported that the tryptamine analogues have lipid solubilities in the order: tryptamine-S > tryptamine-1-Me > tryptamine; the pK_a values and percent ionized at pH 7.4 for the three agonists are virtually identical. Thus, the differences in pharmacological activity described in this paper cannot be due merely to physicochemical differences; therefore, the differences in potency must be due to differences in the mechanism(s) by which these agonists exert their effect on blood pressure. It has been shown that tryptamine does cross the blood-brain barrier (Erspamer, 1961). The physicochemical characteristics of the two analogues indicate that they should also cross the barrier. Thus, a central component may be involved. From the data presented here, it is impossible to speculate as to what type of receptor or combination of receptors is involved.

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