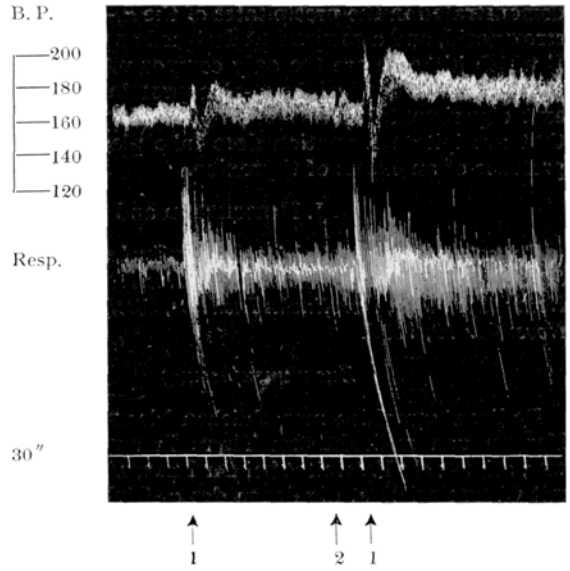
Some Biological Properties of two Fluoro-Derivatives of Tryptamine

In the present communication some biological properties of two fluoro-derivatives of tryptamine, namely 5-fluorotryptamine hydrochloride and 4-fluoro-7-methyltryptamine, are described[1]. It is shown that they closely resemble the parent compound, tryptamine, in many respects. A similar parallelism between certain derivatives of tryptamine and tryptamine itself has been reported recently by VANE[2].

Methods: The following substances were used: 5-fluorotryptamine hydrochloride (5-FT)[3], 4-fluoro-7-methyltryptamine (4F-7M), tryptamine hydrochloride (T), and 5-hydroxytryptamine creatinine sulphate (5-HT).

The toxicity of the first three was tested on male white mice of 20 g body weight, when injected subcutaneously. Dilutions were made in saline, 4F-7M being neutralised in advance by an equimolar amount of hydrochloric acid. The LD_{50} was determined by the log probit method[4]. All quantities are given in terms of the free base. Dogs, mongrels of both sexes (22 animals), were anesthetised with chloralose. The blood pressure was recorded from the right carotid artery with a mercury manometer, and the respiration by a rubber pneumograph. Injections were made through a metallic cannula placed in the jugular vein. To test the central effects in the unanesthetised animal, a permanent cannula was placed in the lateral ventricle of 10 dogs according to the method of HALEY and DICKINSON[5], and mice were injected intracerebrally using the technique of HALEY and MCCORMICK[6]. A maximum volume of 0·5 ml was introduced into the dogs and 0·05 ml into the mice.

Results: The LD_{50} in mice, by the subcutaneous route, was found to be 439 mg/kg for 5-FT, 320 mg/kg for 4F-7M, and 504 mg/kg for T. The symptoms of poisoning with lethal doses were piloerection, obnubilation, lachrimation, bradypnoea with cyanotic tongue, and strong convulsions. Death took place in 2 min to several h after administration. A dose of 320 μg of 5-FT or 4F-7M invariably caused a slight transient hypotensive response in the chloralosed dog and had little effect on the respiration. The protean character of the blood pressure responses to 5-HT in the anesthetised dog (PAGE[7] ERSPAMER[8]) was also seen in our experiments, and when 5-FT or 4F-7M was injected shortly before 5-HT, they always potentiated the latter's response (Fig.). Besides this, 5-FT lowered the rate of disappearance of 5-HT in *in vitro* experiments, using monoamine oxidase of guinea pig liver mitochondria[9]. A similar synergistic effect of 5-FT towards 5-HT has been observed by QUADBECK and ROEHM[10] on the isolated guinea pig intestine. The intracerebral injection of 250 μg of 5-FT into mice immediately produced a stuporous state, similar to that observed by HALEY[11,12] after the injection of smaller doses (10–30 μg) of 5-HT. After the intraventricular injection into dogs of 800 μg/kg T, 1 mg/kg 5-FT or 2 mg/kg 4F-7M, the animal fell into a catatonic-like state similar to that observed by SACCHI *et al.*[13] after the injection of 5-HT via the cisterna magna into dogs, and these results were confirmed by us using the intraventricular cannula. It was of interest to observe the loss of muscular tone which permitted the placing of the dog into abnormal positions, as also seen in the cat by FELDBERG and SHERWOOD[14], GADDUM and VOGT[15], but not by BRADLEY[16]. T also caused defecation of fluid stools, strong rectal tenesmus, and salivation.



Effects of 5-HT and 5-FT on blood pressure and respiration in the chloralosed dog (♂ 11·5 kg)
At 1: 172 μg 5-HT At 2: 320 μg 5-FT

Conclusion: The two fluoro-derivatives of tryptamine studied appear to be more toxic than tryptamine itself. Whilst they themselves, in the doses considered, have only a slight effect on the blood pressure and respiration of the dog, they synergise the responses obtained with 5-HF when injected shortly before this substance, perhaps by preventing the rapid oxidation of 5-HT as seen in *in vitro* experiments. T, 5-FT and 4F-7M are able to produce central effects, when injected intracerebrally, similar to those of 5-HT, but only in larger doses.

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Résumé

La toxicité de la fluoro-5-tryptamine et de la fluoro-4-méthyl-7-tryptamine, ses effets centraux et son influence sur la pression artérielle et la respiration ont été étudiés sur les chiens et souris.

[1] We wish to thank Dr. Z. PELCHOWICZ for supplying these substances.

[2] J. R. VANE, Brit. J. Pharmacol. *14*, 87 (1959).

[3] Z. PELCHOWICZ and E. D. BERGMANN, J. chem. Soc. *1959*, 847.

[4] D. J. FINNEY, *Probit Analysis* University Press, Cambridge, 1952).

[5] T. J. HALEY and R. W. DICKINSON, J. Amer. Pharm. Ass. (Sci. Ed.) *45*, 432 (1956).

[6] T. J. HALEY and W. G. MCCORMICK, Brit. J. Pharmacol. *12*, 12 (1957).

[7] I. H. PAGE, *5-Hydroxytryptamine* (Pergamon Press 1958), p. 93.

[8] V. ERSPAMER, A. M. A. Arch. int. Med. *90*, 505 (1952).

[9] A. CHARI-BITRON, unpublished results.

[10] G. QUADBECK and E. ROEHM, Z. physiol. Chem. *297*, 229 (1954).

[11] T. J. HALEY, Acta pharmacol. toxicol. *13*, 107 (1957).

[12] T. J. HALEY, J. Amer. Pharm. Ass. (Sci. Ed) *46*, 428 (1957).

[13] U. SACCHI, L. GARELLO, G. DOLCE, and F. BANAMINI, Boll. Soc. Ital. Biol. Sper. *32*, 179 (1956).

[14] W. FELDBERG and S. L. SHERWOOD, J. Physiol. *123*, 148 (1954).

[15] G. H. GADDUM and M. VOGT, Brit. J. Pharmacol. *11*, 175 (1956).

[16] P. B. BRADLEY, *5-Hydroxytryptamine* (Pergamon Press 1958), p. 214.