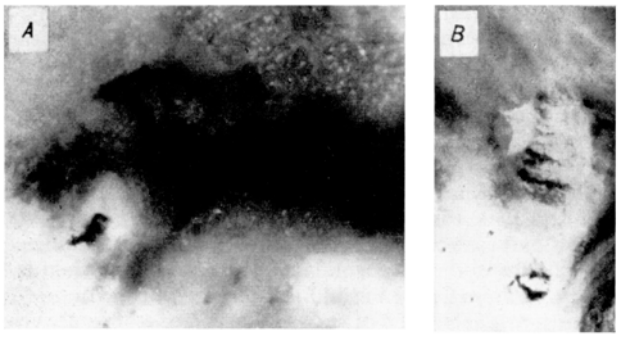

Fig. 1. Part of the lung wall near the renal pore of specimens injected with Indian ink (× 20). A, a string of ink protrudes from the renal pore area. B, opened renal canal; the hemal pore lies at the edge of the renal aperture.

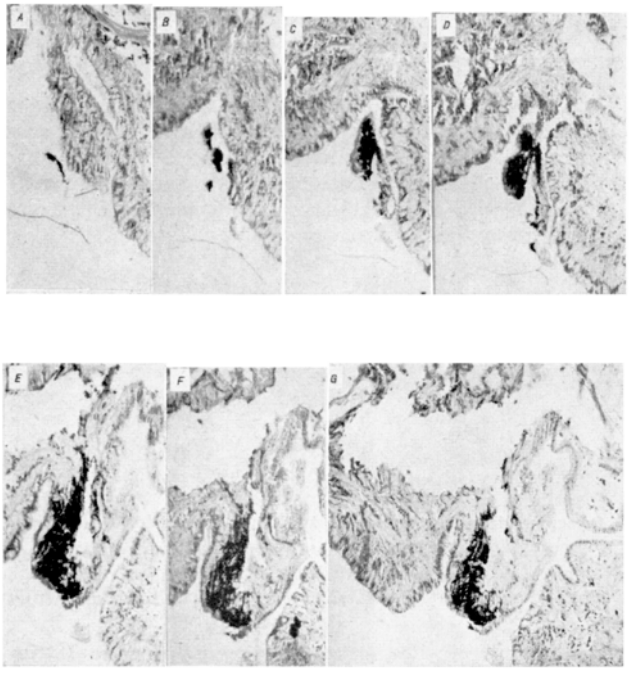

Fig. 2. Sections of the renal tube area (× 140). The ink can be followed from the lung cavity (A, B) via the hemal pore (C, D) to the spongious tissue slits (E, F), which communicate with the hemocoel (G). The renal opening and the renal canal can be seen in the right parts of C–G.

dissected. The tissue around the renal canal was black. However, the lumen of the renal duct was unstained, but, as illustrated by Figure 1A, a string of ink protruded from the renal pore area. When the renal duct was opened longitudinally it was found that the ink emerged from a very small opening located at the edge of the renal pore (Figure 1B). A microscopic study of a specimen injected with Indian ink showed, as can be seen in Figure 2, that this opening is connected via an extremely spongious system of narrow tissue slits with the hemolymph-filled sinuses in the lung wall. Figure 2 (C–F) demonstrates also that this opening is located adjacent to the renal pore in a common indentation of the lung wall.

In the sections, the ink can be seen only in the opening and in the spongious tissue, whereas the sinus is devoid of ink. This is most probably due to the fact that the blood circulation continued for some time during the narcotization period following the injection, so that the non-extruded part of the ink circulated all through the body and concentrated particularly around the kidney (Figure 1).

A final proof of the existence of the *hemal pore* was obtained when Indian ink was injected in blood sinuses of excised pieces of the renal tube area of the lung roof: the ink emerged from the pore.

It is concluded that *Lymnaea stagnalis* has the ability to discharge a large quantity of its hemocoelic blood via a special mechanism. The question of the physiological significance of this is answered, preliminarily, in the following way. Under ordinary conditions, much water continuously enters the body through the skin and the gut, and an equal quantity is eliminated by the kidney. To a large extent the shape of the head and foot is maintained by blood pressure, and during normal life these body parts are mostly extended. However, under sudden emergency conditions, for instance during the attack by a predator or when the snail meets unfavourable substances, the animal retracts very deeply into its shell and produces much mucus. It is clear that such heavy and often rapidly executed contractions are facilitated by the presence of an emergency outlet for the blood. In short, it is supposed that the hemal pore and perhaps also the tissue slits are normally closed, and are used only during violent body contractions.

Zusammenfassung. *Lymnaea stagnalis* verliert nach starker Reizung Blut aus einem der Nierenöffnung dicht anliegenden hämalen Porus, der in Verbindung mit dem System der Blutsinusse steht.

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Department of Zoology, Free University, Amsterdam (The Netherlands), January 15, 1965.

Studies on a Compound Antagonistic to 5-Hydroxytryptamine

It is well established that 5-hydroxytryptamine (5-HT) induces foetal death in various phases of pregnancy[1–3] when administered to pregnant rodents. It is also known that various compounds with anti-enteraminic activity are able to inhibit this effect[1,3,4]. Just recently a new compound, 1-methyl-8β-carbobenzyloxy-aminomethyl-10α-ergoline (MCE), has been synthesized in our laboratories[5]. Its general pharmacological properties have been described extensively elsewhere[6,7].

The effect of anti-enteraminic active compounds upon the survival of foetuses whose mothers have been treated with 5-HT is of high interest. Some authors have identified the 5-HT or analogues as one of the factors involved in human toxaemia during pregnancy[8]. Stimulated by this hypothesis we have studied the activity of MCE in pregnant rats treated with 5-HT.

Methods. Female Sprague-Dawley rats received 2.5 mg 5-HT creatinine sulphate, s.c., on day 19 of the pregnancy. The test compound with anti-5-HT potency was administered s.c. in a single dose at various intervals before the 5-HT (3 h, 24 h, 72 h, 7 days, 14 days) or simultaneously; the doses are indicated in the Figures. The rats were sacrificed 6 h after the 5-HT injection. The uteri were taken out and their contents inspected and the number of living foetuses determined. Their number varied from a minimum of 20 to a maximum of 130 for each experimental group. MCE has been contrasted with 1-methyl-*d*-lysergic acid-butanolamide (UML-491), a compound already known for its anti-enteraminic activity.

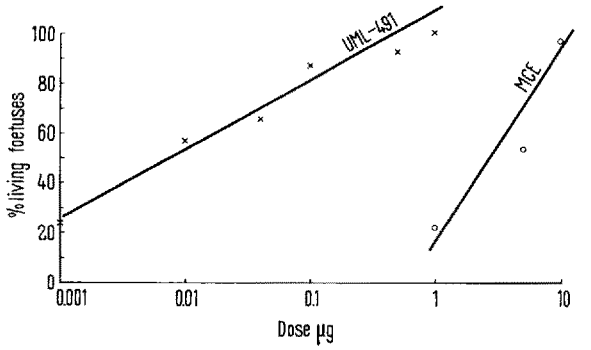

Fig. 1. Effect of UML-491 and MCE upon the survival of foetuses after treatment of the mother with 2.5 mg of enteramine-creatinine sulphate. (Simultaneous administration.)

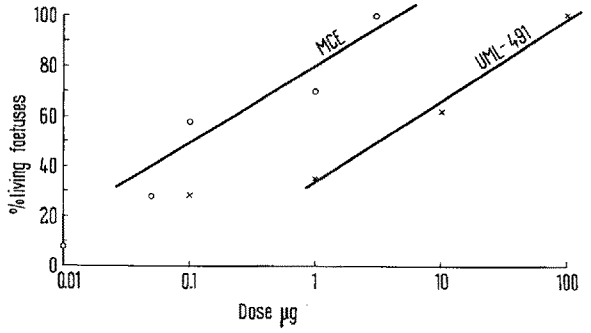

Fig. 2. Same as Figure 1: treatment carried out 3 h before.

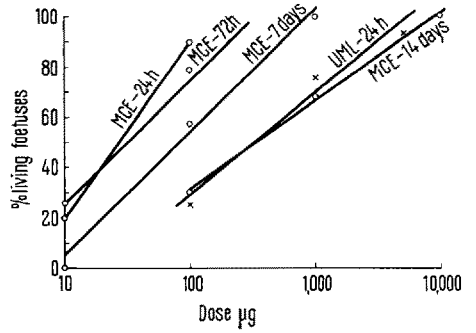

Fig. 3. Same as Figure 1: treatment carried out at various time intervals.

Results. 2.5 mg of 5-HT-creatinine sulphate leads to a foetal mortality of 73.3% (56.8–100%). MCE as well as UML-491 counteract strongly the deleterious effect of 5-HT. Although this effect is represented by an 'all-or-none' recording, it may be successfully utilized if a sufficient number of animals is employed, and will lead to a good correlation between dose and response.

An acute effect is seen when MCE and UML-491 are administered simultaneously with the 5-HT (Figure 1). The first compound has its maximal effect at the dose of 10 µg, whereas the second maintains 90% of the foetuses alive at the dose level of 0.1 µg.

If the compounds are injected 3 h before the 5-HT, the potency of MCE is considerably increased (Figure 2), and is decreased only very slowly (Figure 3) if the interval between the administration of the anti-5-HT compounds and 5-HT is augmented: thus MCE given 14 days before 5-HT shows the same potency as UML-491 after 24 h.

It is evident that the high activity of UML-491 is limited to a short period, whereas MCE reaches its maximal effect slowly and will maintain it for a very long time.

These results confirm the data published elsewhere[6] on other experimental models. The relatively late onset of the maximal effect of MCE and its prolonged activity may be due to the following explanation. It seems to be fairly well established that UML-491 and MCE exert their anti-5-HT activity by the blockade of receptor groups. It might be theoretically possible that MCE becomes active after passing metabolization, which would explain the late onset of the maximal effect. The active metabolite itself might block the receptors more efficiently and occupy them for a long period of time and thus exert an effect characterized by its long duration. Our theoretical conclusion will have to be confirmed by further studies[9].

Riassunto. La 1-metil-8β-carbobenzilossi-aminometil-10α-ergoline (MCE) impedisce la morte dei feti in ratte gravide trattate con enteramina (5-HT). L'effetto massimo è ottenuto quando l'MCE è somministrato 3 h prima della 5-HT, ma si manifesta anche 14 giorni dopo una iniezione del composto.

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[9] Acknowledgment: The authors would like to express their thanks to Sandoz, Basel (Switzerland) for the supply of UML-491.