geprüften tumorhemmenden Stoffes Faktoren wichtig sind, die nicht tumorspezifisch sein können.

Es ist deshalb die Bedeutung allgemeiner Gewebewirkungen und Gewebewachstumsfaktoren für die Wirkung von tumorhemmenden Stoffen näher abzuklären. Wir werden auf analoge Befunde mit anderen tumorhemmenden Stoffen zurückkommen.

R. Meier, P. A. Desaulles und P. Loustalot

Wissenschaftliche Laboratorien der CIBA Aktiengesellschaft, den 15. Dezember 1955.

Summary

The action of Triethylenmelamine, an anti-tumour substance, was investigated on tumourgrowth and on development of the foreign body granuloma comparatively.

It was found that this substance induces in both cases a similar dosis-dependent inhibition of growth.

As the inhibiting action of Triethylenmelamine can even be demonstrated on rapidly growing normal tissues, it is questionable whether the antagonistic action against tumour can be designed as tumour-specific.

Observations on the 5-Hydroxytryptamine (Enteramine) Release Caused by Reserpine in the Rat

Shore *et al.*[1] and Pletscher *et al.*[2] have recently shown that reserpine given intraperitoneally causes in the dog a marked increase in the rate of urinary excretion of 5-hydroxyindoleacetic acid-like material (5-HIAA), and in the rabbit a conspicuous, progressive reduction in the 5-hydroxytryptamine (5-HT) content of the gastrointestinal tract.

The experiments described in this preliminary communication confirm and extend the findings of the above investigators.

(a) 14 groups of 4 rats each, weighing 130–200 g, were injected intraperitoneally with distilled water (controls) or with 5 mg/kg reserpine. The animals were killed by decapitation at varying intervals after the injection and acetone extracts of serum, gastrointestinal tract, spleen and brain were prepared according to our usual procedure[3]. The 5-HT content of this material was assayed on the rat uterus preparation[4].

3 groups of 4 rats each were injected intraperitoneally with 1 mg, 0·3 mg and 0·1 mg/kg of reserpine, respectively, and killed after 16 h. The material was treated and studied as above.

The results are shown in Table I.

Two interesting facts emerge from the tabulated data: the first is that the decrease in the 5-HT content of serum (= blood platelets) and spleen is much more conspicuous, and considerably more durable than that in the 5-HT content of the gastrointestinal tract and brain; the second that a single dose of 0·1 mg/kg of reserpine is sufficient to cause the release of more than 30% of the normal 5-HT from the platelets and the spleen.

Table I

Treatment and time of survival	5-HT content, in µg of free base, per g of fresh material			
	Serum	Spleen	Gastro-intest. tract	Brain*
Distilled water 6 h . . .	0·60	1·61	2·07	0·23
Distilled water 40 h . . .	0·65	1·71	2·15	0·28
Reserpine 5 mg 1 h . . .	0·43	2·15	1·50	0·16
Reserpine 5 mg 2 h . . .	0·19	1·03	2·02	0·10
Reserpine 5 mg 4 h . . .	0·07	0·57	1·59	0·18
Reserpine 5 mg 6 h . . .	0·06	0·27	1·30	0·16
Reserpine 5 mg 10 h . . .	0·03	0·15	1·59	0·13
Reserpine 5 mg 20 h . . .	0·02	0·09	1·60	0·20
Reserpine 5 mg 40 h . . .	0·06	0·13	1·50	0·12
Reserpine 5 mg 3 days . . .	0·12	0·38	1·38	0·30
Reserpine 5 mg 4 days . . .	0·19	0·53	2·02	0·40
Reserpine 5 mg 6 days . . .	0·34	0·86	1·42	0·32
Reserpine 1 mg 16 h . . .	0·05	0·12	1·42	0·22
Reserpine 0·3 mg 16 h . . .	0·17	0·58	2·15	0·30
Reserpine 0·1 mg 16 h . . .	0·38	1·03	1·45	0·40

* The data concerning the brain have been obtained by P. Correale (forthcoming publication).

(b) To investigate whether exogenous 5-HT is capable of preventing the 5-HT release caused by reserpine, a high dose of 5-HT was given subcutaneously to 3 groups of 4 rats each, contemporaneously with an intraperitoneal dose of 2 mg, 1 mg, and 0·5 mg/kg of reserpine, respectively. All the animals of the group treated with 2 mg of reserpine died after 8–14 h; the others were killed after 24 h.

The results are summarized in Table II.

Table II

Treatment	5-HT content (µg/g)			
	Serum	Spleen	Gastro-intest. tract	Brain
Distilled water	0·68	1·42	2·30	0·44
Reserpine 1 mg + 5-HT 25 mg	0·57	2·58	1·96	0·20
Reserpine 0·5 mg + 5-HT 25 mg	0·74	3·62	2·25	0·40
5-HT 25 mg	1·23	2·65	–	–

It appears evident that pretreatment with massive doses of exogenous 5-HT is capable of maintaining high 5-HT levels especially in serum and spleen, in spite of the simultaneous administration of doses of reserpine which are very effective in reducing these levels. Further experiments are needed to elucidate the mechanism of this apparent competition between reserpine and 5-HT.

(c) 5 groups of 16 rats each, weighing 200–400 g, were distributed into 20 diuresis cages. After normal urine had been collected over a 3 h control period, 4 groups of rats were injected intraperitoneally with 5 mg/kg of reserpine and 1 group with distilled water (0·5 ml/100 g). Urine collection was then continued for 4 successive periods, each of 3 h. The 5-HIAA content of the different urine

[1] P. A. Shore, S. L. Silver, and B. B. Brodie, Science *122*, 284 (1955).

[2] A. Pletscher, P. A. Shore, and B. B. Brodie, Science *122*, 374 (1955).

[3] V. Erspamer, Arch. exper. Pathol. u. Pharmakol. *196*, 343 (1940); J. Physiol. (in press).

[4] V. Erspamer, Arch. exper. Pathol. u. Pharmakol. *196*, 343 (1940); J. Physiol. (in press).; Rendiconti scient. Farmitalia *1*, 1 (1954).

Table III

Treatment	5-HIAA content of urine (in μg per kg body weight)				
	Control period	Collection periods after treatment			
		0–3 h	3–6 h	6–9 h	9–12 h
Distilled water . .	10	13	12	13	10
Reserpine	11	20	58	20	12
Reserpine	14	20	50	20	13
Reserpine	10	20	54	40	10
Reserpine	13	18	52	32	12

samples was determined according the method described in a previous paper[5].

The results are shown in Table III.

It is easy to see from the tabulated data that the maximum excretion of 5-HIAA occurs in the second collection period, in which the urine content of the metabolite is more than fourfold, as compared with that of urine of untreated rats. The total 5-HIAA excreted by rats injected with reserpine exceeds that of control rats by 55–76 μg/kg.

(d) 2 groups of 4 rats each were injected subcutaneously with 25 mg/kg of 5-HIAA and killed after 30 min and 2 h respectively; 4 groups of 4 rats each were treated intraperitoneally with 1 mg and 5 mg/kg of 2-brom-*d*-lysergic acid diethylamide, coded *BOL* 148, and killed after 1 and 2 h, respectively; 3 groups of 5 rats each were given intraperitoneally daily injections of 10 mg/kg dibenamine and killed 8 h after the 1st, the 3rd and the 11th injection, respectively; finally, 4 groups of 4 rats each were given intraperitoneally chlorpromazine 2 and 10 mg/kg and killed after 5 and 24 h, respectively.

No significant changes in the 5-HT content of serum, spleen and gastrointestinal tract could be observed in these groups of animals.

The experimental results described in this communication will be discussed in detail in the paper *in extenso*.

I wish to thank the Sandoz and CIBA Research Laboratories, Basle, for generous samples of *BOL* 148 and reserpine (Serpasil), respectively. 5-HT creatinine sulphate and 5-HIAA were synthetized in the Farmitalia Research Laboratories, Milan.

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Institute of Pharmacology, University of Bari, Italy, November 29, 1955.

Zusammenfassung

Bei ausreichender Dosierung ist Reserpin imstande, eine praktisch vollkommene Freisetzung des 5-Oxytryptamins (5-OT) aus den Blutplättchen und der Milz zu verursachen und eine partielle Freisetzung aus der Magen-Darmschleimhaut und dem Gehirn. Die Ausgangswerte werden dann nur langsam erreicht. 5-OT exogener Herkunft hindert die reserpinbedingte Ausschüttung des endogenen 5-OT.

[5] V. ERSPAMER, J. Physiol. *127*, 118 (1955).

Respiratory Changes in Decorticate Cats Following Transverse Sections Through the Hypothalamus

During acute experiments in this laboratory when transsections through the hypothalamus were made in 60 decorticate cats with a view to prepare diencephalic cats, approximately 20% of these animals exhibited very hurried and rather shallow respirations soon after the transverse section. Such changes in respiration were not seen in decerebrate, but were observed in diencephalic cats only.

This led to consideration of the possibility of the transverse section in these animals being at such a level whereby some respiratory centres were released from rostral inhibitory control.

Previous workers have obtained fairly comparable results form the stimulation, in man, of different parts of the hippocampus–mammillary body–anterior thalamic nuclei–cingulate gyrus complex[1], apnoea being a constant feature of stimulation of these areas besides facilitation or inhibition of somato-motor activity and autonomic changes etc. Recently SEGUNDO *et al.*[2] observed that electrical stimulation of the fornix produced apnoea and other effects similar to that obtained with stimulation of structures between which it formed an important link; they further added that the "excitation of the 'anterior periventricular' region in man induced marked acceleration of the respiratory rate and diminution of its amplitude, the respiratory changes resembling that seen in the polypneic panting evoked from this region in animals[3]. Obviously, decending connections from this region pass to pontobulbar levels controlling respiratory activity and possibly subservs the regulation of body temperature[4]".

It thus appears possible that the transsections carried out during our experiments were through a plane rostral to the periventricular respiratory centres, thereby releasing them from inhibitory control. Further work on the subject is in progress[5].

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Department of Pharmacology, School of Tropical Medicine, Calcutta, October 18, 1955.

Zusammenfassung

Anscheinend bedingt die frontale Durchschneidung des Hypothalamus in der diencephalischen Katze eine Loslösung des vorderen periventrikulären Atemzentrums von höherer (rostraler) hemmender Kontrolle.

[1] W. P. CHAPMAN, R. B. LIVINGSTON, and K. E. LIVINGSTON, Arch. Neurol. Psychiat. Chicago *62*, 701 (1949). – B. R. KAADA and H. J. JASPER, Arch. Neurol. Psychiat. Chicago *68*, 609 (1952). – W. T. LIBERSON, W. B. SCOVILLE, and R. H. DUNSMORE, J. EEG clin. Neurophysiol. *3*, 1 (1951).

[2] J. P. SEGUNDO, R. ARANA, E. MIGLIARO, J. E. VILLAR, A. GRACIAGUELFI, and H. GRACIA AUSTT, J. Neurophysiol. *18*, 96 (1955).

[3] H. W. MAGOUN, F. HARRISON, J. R. BROBECK, and S. W. RANSON, J. Neurophysiol. *1*, 101 (1948).

[4] J. F. FULTON, *Physiology of the nervous system*, 3rd ed. (Oxford Univ. Press, 1949).

[5] In a recent communication to the writers, Dr. JOHN F. FULTON informs that his colleague at the Yale University School of Medicine, Dr. PAUL MACLEAN, has also noticed similar respiratory changes in the course of his experiments.

[6] Vorstand des Pharmakologischen Instituts der Universität Graz, Österreich; 1954/55 WHO-Professor, Department of Pharmacology, School of Tropical Medicine, Calcutta.