degeneration due to changes of the endolymph, secondary to atrophy of the stria[12].

Zusammenfassung. Nachweis einer Melanin-Affinität ototoxischer Medikamente im Zusammenhang mit histopathologischen Änderungen in der Stria pigmentierter Tiere, nicht aber bei Albinos, durch Kanamycin.

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Duodenal Ulcer in Rats by 3-Allyl-5-isobutyl-2-thiohydantoin and its Related Compound

Although many drugs and chemicals can cause gastric ulcer in animals, few compounds are known consistently to induce duodenal ulcer. Infusion of gastrin, either alone or in combination with other secretagogues such as histamin and carbachol, can produce duodenal ulcer in various animal species[1-3]. SZABO et al.[4] reported production of solitary, often perforating, duodenal ulcers in female rats by injections of propionitrile. While studying the acute toxicity of 3-allyl-5-isobutyl-2-thiohydantoin, an anti-convulsant[5], we incidentally found that a single administration of this compound could consistently induce duodenal ulcer in rats.

Materials and methods. Male Wistar rats weighing around 120 g were kept in mesh-bottomed metalic cages to avoid coprophagia. The test compound, 3-allyl-5-isobutyl-2-thiohydantoin, was suspended in 10% aqueous solution of gum acacia such that 1.0 ml contained the necessary amount for a single administration, and given to rats after overnight fasting. Fasting was continued for 24 h after medication. Experiments were conducted in the following series:

In the first experiment 6 groups of 5 rats each received an oral or s.c. administration of the compound in the dose levels shown in Table I and were killed 24 h after administration by exsanguination from the carotid artery under ether anesthesia. The stomach and duodenum were excised, opened along the greater curvature, spread on a rubber board and examined with a binocular microscope. Another 10 rats served as control and were killed 24 h after oral or subcutaneous administration of 1.0 ml of the suspension vehicle.

In the second experiment 10 rats received subphrenic vagotomy[6] under pentobarbital anesthesia, and another 10 rats were submitted to sham operation. 10 days after the operation, they were given a s.c. injection of either 175 mg/kg of the compound or 1.0 ml of the suspension vehicle and killed 24 h after injection. The stomach and duodenum were examined in the way mentioned above.

In the third experiment, the 11 compounds shown in Table III were tested for the ulcerogenic effect. They were suspended in 10% aqueous solution of gum acacia and given to rats orally or s.c. in the dose levels shown in Table III. The stomach and duodenum were examined 24 h after administration.

Results and discussion. Ulceration of the duodenum occurred in 21 out of 30 rats given 3-allyl-5-isobutyl-2-thiohydantoin, while in control rats the stomach and duodenum had a normal appearance. The ulcers were elongated, often in pairs and located on the anti-mesenteric aspect of the duodenum about 6 to 10 mm caudal from the pylorus. Severity of the duodenal lesion was apparently dose-dependent (Table I). Perforating ulcer with consequent peritonitis occurred in 4 out of 20 rats given 250 mg/kg or more of the compound. Besides, in thiohydantoin-treated rats the stomach was distended with accumulation of acidic fluid (pH 1 to 2), and small

Table I. Occurrence of duodenal ulcer in rats following a single administration of 3-allyl-5-isobutyl-2-thiohydantoin

Route of administration	Dose (mg/kg)	No. of rats	Grades of duodenal ulcer[a] —	+	++	+++
Subcutaneous	0	5	5	0	0	0
	125	5	4	1	0	0
	250	5	1	1	2	1
	500	5	0	0	1	4 (1)[b]
	0	5	5	0	0	0
Oral	125	5	4	1	0	0
	250	5	0	0	1	4 (1)
	500	5	0	0	1	4 (2)

[a] — no ulcer; + small shallow ulcer of up to 2 mm in diameter; ++ elongated or linear ulcer of 3 to 6 mm in length; +++ elongated or linear ulcer of 6 mm or longer in length. [b] Numerals in parentheses indicate the number of rats with perforating ulcer.

Table II. Inhibitory effect of vagotomy on occurrence of duodenal ulcer in rats by 3-allyl-5-isobutyl-2-thiohydantoin

Treatment	Dose (mg/kg)	No. of rats	Grades of duodenal ulcer[a] —	+	++	+++
Vagotomy	0	5	5	0	0	0
Vagotomy	175	5	5	0	0	0
Sham operation	0	5	5	0	0	0
Sham operation	175	5	0	2	2	1

[a] See the note of Table I.

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Table III. Ulcerogenic action of thiohydantoins, thioamides and mercaptohiazoline in rats

Compounds	Dose (mg/kg)	Route	No. of rats	Grades of duodenal ulcer[a] —	+	++	+++
3-Allyl-5-isobutyl-2-thiohydantoin	175	s.c.[c]	5	0	0	1	4 (1)[b]
3-Allyl-5-isobutyl-hydantoin	250	s.c.	5	5	0	0	0
3-Ethyl-5-isobutyl-2-thiohydantoin	250	s.c.	5	0	3	0	2 (1)
3-Ethyl-5-isobutyl-hydantoin	250	s.c.	5	5	0	0	0
Thiobenzamide	300	s.c.	5	0	0	2	3 (1)
Benzamide	1000	s.c.	5	5	0	0	0
α-Ethylthioiso-nicotinamide	300	oral	5	0	1	1	3
Thioacetamide	500	s.c.	5	5	0	0	0
Thiobarbituric acid	500	s.c.	5	5	0	0	0
Thiouracil	500	s.c.	5	5	0	0	0
Mercaptothiazoline	500	s.c.	5	0	0	3	2

[a] See the note of Table I. [b] Numerals in parentheses indicate the number of rats with perforating ulcer. [c] s.c., subcutaneous.

shallow ulcers frequently appeared in the antrum. These pathological features resemble those of the gastroduodenal lesion in rats caused by infusion of secretagogues[3]. Therefore, it is reasonable to assume that hypersecretion of acid from the parietal cells is also responsible for the pathogenesis of thiohydantoin-induced duodenal ulcer This assumption is supported by the fact that vagotomized rats were quite refractory to the ulcerogenic effects of the compound (Table II).

As shown in Table III, duodenal ulcers could be induced in rats not only by thiohydantoins but also by other compounds such as thiobenzamide, α-ethylthioisonicotinamide and mercaptothiazolin, while 3-allyl- or 3-ethyl-5-isobutylhydantoin, benzamide, thiouracil or thiacetamide did not produce any gastroduodenal alterations. This finding may be relevant to the clinical evidence which indicates the occurrence of gastric distress or abdominal discomfort by α-ethylthioisonicotinamide[7,8] or 3-allyl-5-isobutyl-2-thiohydantoin[9].

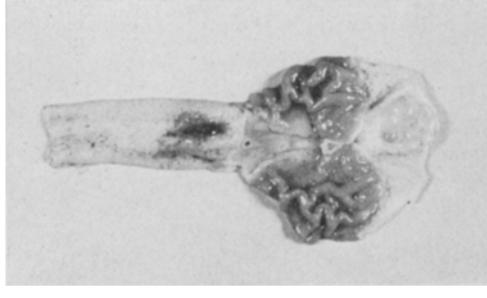

Fig. 1. The stomach and duodenum from a rat 24 h after a s.c. injection of 250 mg/kg of 3-allyl-5-isobutyl-2-thio-hydantoin. An elongated deep ulcer and small shallow ulcers are seen in the duodenum. 3 small ulcers appear in the antrum of the stomach.

Recently Cook et al.[10] and Malen et al.[11] have shown that certain thiocarboxamides such as 2-phenyl-2-(2-pyridyl) thioacetamide and 2-(2-pyridyl) butanothioamide possess a specific gastric antisecretory property in animals. Lee et al.[12] have demonstrated antigastrin activities of 2-phenyl-2-(2-pyridyl)-thioacetamide and allied compounds in animals. In contrast with the present finding, these data suggest the possibility that certain thiocarboxamides possess anti-ulcer effects. It is of interest that these structurally-related compounds can exert different effects on gastroduodenal physiology. At present, the structure-activity relationship remains to be established.

Zusammenfassung. Es wird gezeigt, dass in Ratten mit 3-Allyl-5-isobutyl-2-thiohydantoin und ähnlichen Substanzen Duodenalulzera hervorgerufen werden können und dass die Bildung von Ulzera durch eine vorhergehende Vagotomie verhütet werden kann.

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Evidence that Morphine Increases Dopamine Utilization in Corpora Striata of Rats

In rats, Kuschinsky and Hornykiewicz[1] observed a dose-dependent increase of striatal homovanillic acid (HVA) concentration after morphine treatment. This effect was explained by an increased dopamine (DA) turnover; other explanations were rather unlikely. However, since no absolutely safe method to estimate brain dopamine turnover exists as yet, I decided to study striatal dopamine turnover by a second, independent approach. Andén et al.[2] used blockade of catecholamine synthesis by α-methyl-*p*-tyrosine, a potent inhibitor of tyrosine hydroxylase[3], as a tool for measuring turnover in the catecholamine neurons. Alter inhibition of dopamine synthesis, the rate of depletion should be proportional to the 'impulse flow' within the neuron: the higher