pressor response to 5-HT (8 experiments). Furthermore, it is known that central injection of hexamethonium, in a similar dose range as in the present experiments, blocks the pressor response to centrally injected carbachol in rats[9]. On the other hand, all doses of methysergide between 7 and 10 ng abolished the hypertensive effect of 5-HT (Figure 1; 6 experiments). However, in a separate experimental group, methysergide (7–10 ng) did not appreciably affect the increase in arterial blood pressure caused by acetylcholine (6 experiments). Accordingly, the pressor response to i.vent. administration of 5-HT was selectively blocked by methysergid.

The preliminary experiments have shown that the pressor response to 5-HT was not appreciably altered in reserpinized rats (6 experiments). However, further experiments are necessary in order to establish the real nature of the peripheral mechanism mediating the hypertensive response to 5-HT.

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Hexobarbital Action in Rats with Flavonoid-Deficiency

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Summary. In flavonoid-deficient rats, hexobarbital-sleeping times are prolonged. The hexobarbital concentrations in brain, liver and plasma are increased. These results are discussed as a consequence of an impaired drug metabolism.

Feeding rats a diet lacking flavonoids raises the pentobarbital-induced sleeping time (Földi and Földi-Börcsök[1]). The problem arose as to whether the action other drugs with effects on the central nervous system is also changed.

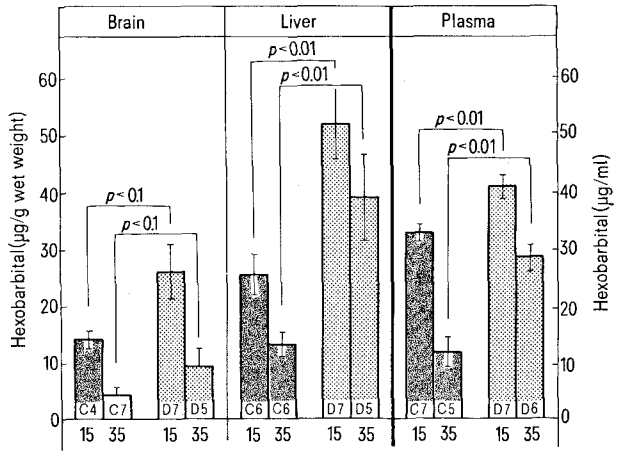
Therefore rats on a diet lacking the flavonoids were injected with hexobarbital. Their sleeping times were estimated, and 15 and 35 min after the injection measurements of the barbiturate in brain, liver and plasma were performed. Such measurements give some information about the disappearance of the drug from these 3 compartments, and therewith about the metabolic rate leading to the inactivation of the hexobarbital (Bush and Weller[2]).

Materials and methods. In the course of September 1975, experiments were performed on male Sprague-Dawley rats with a body weight of 425 ± 10 g ($\bar{x} \pm s_{\bar{x}}$, $n = 26$). The ages and the body weights of flavonoid-deficient (FD) and control rats, respectively, did not differ. The FD-animals were fed for more than 4 months with the diet. These rats, as well as the control animals on a standard diet, were kindly given by Prof. M. Földi. The detailed conditions of their nutrition are described by Földi and Földi-Börcsök[1].

The rats were injected with hexobarbital-Na in a dose of 50 mg/kg i.e. 1 ml/kg into a tail vein. The injection time was about 15 sec. The time interval from the end of the injection till the moment when the rats where put on one side, turned back on their hind legs, was measured and called sleeping time.

Estimations of hexobarbital in brain, liver and plasma were performed by a gaschromatographic procedure (for details see Endell and Seidel[3]). Results are given as mean ± standard error of mean ($\bar{x} \pm s_{\bar{x}}$). Statistical analysis of the significance of differences between two means was performed using the *t*-test.

Results. FD-rats treated i.v. with hexobarbital slept longer than the controls. While the sleeping time in the latter group was 13.4 ± 0.9 min ($n = 7$) 4 of 6 FD-animals still slept when they were decapitated 35 min after the injection of the barbiturate. The sleeping times in the two other FD-animals were 24.6 and 17.6 min, respectively.



Concentrations of hexobarbital in brain, liver and plasma of rats 15 and 35 min, respectively, after injection (50 mg/kg i. v.). Number in the columns: animals/group. C, normally fed animals; D, flavonoid-deficient animals.

The hexobarbital concentrations in brain, liver and plasma 15 and 35 min, respectively, after the administration of the hexobarbital, are shown in the Figure. The FD-animals revealed higher concentrations which decreased more slowly than those in the controls. As hexobarbital is eliminated mainly by metabolic degradation in the liver (Bush and Weller[2]), this may indicate an impaired hexobarbital metabolism.

The means of the quotients 'hexobarbital concentration in brain divided by the concentration in plasma' of single FD-rats, as well as of the controls, were in the same range [15 min: 0.63 ± 0.09 ($n = 7$) versus 0.54 ± 0.14 ($n = 4$); 35 min: 0.37 ± 0.12 ($n = 5$) versus 0.46 ± 0.15 ($n = 5$)].

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Consequently, the distribution of hexobarbital between plasma and brain tissue in the FD-rats remained unaltered; 15 min after injection of the barbiturate, the quotient liver/plasma was for FD-rats higher than that for controls [1.26 ± 0.13 (n = 7) versus 0.79 ± 0.11 (n = 6), $p < 0.01$].

Undoubtedly, this means an accumulation of hexobarbital in the liver of FD-rats, which, however, is scarcely to be expected to shorten the sleeping time. The liver weight amounts only to 5% of the total body weight (HAGEMANN[4]). Therefore, in FD-rats the liver cannot be expected to take up so much more hexobarbital than in normally fed animals that this would reduce the amount of drug available in the brain.

Also 35 min after injection, when the absolute concentrations were still higher in FD-rats, and had not fallen so much as in normally fed animals, the quotients liver/plasma of the experimental and the control group, respectively, were found identical [1.35 ± 0.27 (n = 5) versus 1.38 ± 0.44 (n = 4)].

Discussion. The results show that in FD-rats hexobarbital concentrations in brain, liver and plasma are higher than those in the normally fed animals, and decrease more slowly. This slowed elimination may be explained by an impaired drug metabolism leading to a reduced breakdown of hexobarbital in the liver. A pharmacological consequence would be the prolonged sleeping time, as already found for pentobarbital by FÖLDI and FÖLDI-BÖRCSÖK[1].

To explain the prolonged sleeping times in FD-rats, it is not necessary to take into account a changed brain susceptibility for hexobarbital. Furthermore, in FD-rats and controls, respectively, the same distribution quotients brain/plasma point to the fact that in both groups hexobarbital is found in the brain tissue in the same portion of the plasma concentration. Obviously the blood-brain barrier for hexobarbital, if it exists at all (OLDENDORF[5]), remains in its previous state.

In flavonoid deficiency, the drug metabolizing systems in the liver microsomes may be disturbed. Such damage would fit into a general disturbance of FD-rats. This view is supported by our own observation that within 2 weeks after the transport by car from Salzgitter to Lübeck (about 300 km) 20 of 35 FD-rats died while the same number of control animals survived.

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An Electron Microscopic Study on the Autonomic Innervation of the Rabbit Parotid Gland[1]

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Summary. As visualized in the electron microscope, the parotid gland of the rabbit has a dual innervation. Both adrenergic and cholinergic nerves are equally distributed in the parenchyma and often run together within the same nerve bundle. Nerve terminals are observed not only subjacent to the basement membrane but interposed between the latter and the acinar cells, where they establish a close membrane to membrane contact with the latter.

The rabbit parotid gland, a purely serous gland[3,4], has been widely employed in experimental physiological and pharmacological studies on secretory responses to various stimuli. Moreover, the rabbit parotid gland has been extensively investigated with respect to cellular synthesis and secretion of salivary gland secretory proteins[5,6]. These functional studies have been supplemented by recent recordings of morphometric data concerning the secretory cells[7,8].

However, there is but little information to be obtained in the literature on the distribution of autonomic nerve elements within this gland. The present paper deals with some electron microscopic findings on the relationship between adrenergic and cholinergic nerves and the acinar cells of the rabbit parotid gland.

Materials and methods. Salivary gland tissue was obtained from 4 adult male rabbits of a mixed strain. The animals were killed by an i.v. injection of sodium pentobarbital (Mebumal®, ACO Drug Ltd., Sweden). The parotid glands were rapidly removed, and small tissue slices were fixed for 90 min in icecold 3% $KMnO_4$ in Krebs-Ringer phosphate buffer (pH 7.0). Following fixation, the specimens were rinsed in Ringer solution and contrasted en bloc for 60 min in 1% uranyl acetate[9]. The specimens were dehydrated in graded ethanol solutions followed by propylene oxide and embedded in Epon 812. Ultrathin sections were cut on an LKB Ultrotome, collected on copper grids, contrasted with lead citrate and examined in a Philips EM 300 electron microscope.

Results and discussion. In the connective tissue between the acini throughout the parotid gland, numerous unmyelinated nerves are observed. The nerves generally appear in bundles, each containing several axons completely or partly enveloped by a Schwann cell. With the present technique, it was possible to distinguish between two types of axons on the basis of the appearance of the neuronal vesicles within axonal varicosities. One group of varicosities contains either small, granular vesicles (500–600 Å in diameter), or slightly larger ones (1,000–1,200 Å). These axons represent adrenergic nerves. The other group contains agranular vesicles (500–600 Å); these are cholinergic nerves. The 2 types of axons are often found within the same nerve bundle, i.e. they are enveloped by the same Schwann cell.

Adrenergic as well as cholinergic varicosities are commonly observed subjacent to the acinar cells, separated from the latter by the basement membrane only. However in addition to these extra-acinar nerve terminals, varicosities are also encountered interposed between the acinar basement membrane and the epithelial cells. These intra-acinar nerve endings are completely free of Schwann cell investment, and contain either granular (adrenergic) (Figure 1) or agranular vesicles (cholinergic) (Figure 2). Within contact areas, the axolemma and the secretory cell plasma membrane run parallell and are separated by a roughly 200 Å wide cleft.

With respect to duct cells, the situation appears to be quite different, as no autonomic nerve endings are ob-