Table I. The effect of noradrenaline ($10^{-4}M$) on the oxygen consumption (QO_2) of rat brain cortex slices during ontogeny

Age (days)		$QO_2 \pm$ S.E.M. (0–30 min)	Significance (p)	$QO_2 \pm$ S.E.M. (30–60 min)	Significance (p)
10	Control	12.8 ± 0.5 (6)	—	12.7 ± 0.5	—
	Noradrenaline	13.8 ± 0.8 (6)		13.1 ± 0.7	
20	Control	14.1 ± 0.3 (7)	—	13.9 ± 0.4	—
	Noradrenaline	13.9 ± 0.5 (7)		13.7 ± 0.4	
40	Control	13.5 ± 0.4 (10)	< 0.1	12.7 ± 0.4	—
	Noradrenaline	12.8 ± 0.4 (10)		12.7 ± 0.4	

–, not significant. Number of experiments in parentheses.

Table II. The effect of noradrenaline ($10^{-4}M$) on the oxygen consumption (QO_2) of thyroxine treated rat cortex slices during ontogeny

Age (days)		$QO_2 \pm$ S.E.M. (0–30 min)	Significance (p)	$QO_2 \pm$ S.E.M. (30–60 min)	Significance p	Dosis (μg T_4/kg)
10	Control	13.2 ± 0.5 (6)	—	13.0 ± 0.3	—	3×300
	Noradrenaline	12.5 ± 0.4 (6)		11.7 ± 0.9		
20	Control	13.4 ± 0.4 (8)	< 0.025	13.7 ± 0.5	< 0.1	3×300
	Noradrenaline	14.7 ± 0.3 (8)		15.4 ± 0.6		
40	Control	12.6 ± 0.3 (11)	< 0.01	12.6 ± 0.4	< 0.025	4×700
	Noradrenaline	14.7 ± 0.4 (11)		13.9 ± 0.5		
120	Control	11.2 ± 0.5 (9)	< 0.05	11.8 ± 0.4	< 0.1	5×800
	Noradrenaline	13.0 ± 0.4 (9)		12.9 ± 0.3		

–, not significant. Number of experiments in parentheses.

group in which noradrenaline caused no stimulation of respiration, it may be expected that thyroxine dosage was not optimal. Two different doses: 2×300 μg T_4/kg and 5×300 μg T_4/kg were also tested. Noradrenaline had no effect also in both of the cases.

KRISHNA et al.[1] detected (the dose of thyroxine was similar to that used in this study) that thyroxine increases the amount of adenyl cyclase in the adipose tissue of the adult rat. There is some evidence[5,6] that catecholamines stimulate the adenyl cyclase in the cortex. It is thus possible that the stimulated metabolism caused by increased 3′, 5′-AMP could explain the increased oxygen consumption.

If the control values in Tables I and II are compared with each other, the effect of thyroxine on the respiration of the cortex slices can be seen. FAZEKAS et al.[7] found that thyroxine increases the respiration of juvenile rat cortex slices, which could not be observed in the study in question. Perhaps it is the different thyroxine dosage that causes the difference in the results. RASKIN and FISHMAN[8] found that the Na-content of the brain tissue increases in case of hyperthyreosis, whereas the K-content is decreased. However, there was no difference in the activity of ATP-ase. Perhaps the result is due to a failure of methods because the lowered ATPase activity could explain the small decrease of respiration observed in this study.

Zusammenfassung. Bei mit Thyroxin behandelten Ratten verursachte Noradrenalin eine Stimulierung des Sauerstoffverbrauchs in Cortex-Ausschnitten. Der Wegfall dieser Beobachtung bei normalen Ratten weist auf die Wechselwirkung zwischen Noradrenalin und Thyroxin im Gehirngewebe hin.

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Effect of Oxyphenbutazone on Concentration of Penicillin in Serum

Non-hormonal antiphlogistic therapy with pyrazol derivatives has long been used successfully in the treatment of inflammatory processes, fever and pain. According to LEGLER and BRACHARZ[1], treatment with antiphlogistics of oxyphenbutazone type combined with antibiotics results in a higher antibiotic concentration in the serum. This increase has been ascribed either to inhibition of the tubular secretion[2], or to interaction of pyrazol derivatives

with antibiotics concerning plasma protein binding[3], and might mean an improvement of the effect of antibiotic therapy[4–8].

LEGLER and BRACHARZ[1] carried out 3 trials; with penicillin alone, penicillin plus oxyphenbutazone 0.2 g × 3, and oxyphenbutazone in the same dose as above started 3 days and 7 days, respectively, before commencing treatment with penicillin. The investigations were carried out partly with benzylpenicillin (penicillin G) 500,000 IU i.m., partly with phenoximethyl penicillin (penicillin V) 600,000 + 600,000 IU orally at 4 h intervals. In the first series, oxyphenbutazone, started 3 days before commencing treatment with penicillin G, produced in the same subjects significantly higher penicillin concentrations than those obtained with penicillin G alone, and this was also the case in the other series with penicillin V when treatment with oxyphenbutazone was started 7 days before the administration of penicillin. When in this series the oxyphenbutazone was not started until 3 days before giving penicillin, a higher concentration was reached only in some of the subjects, and then only 6 h after administering penicillin.

The purpose of the present study was to investigate whether the effect reported by LEGLER and BRACHARZ could be demonstrated in a further series of hospitalized patients.

Material and methods. We performed a simple investigation on 14 convalescent patients without signs of renal or gastro-intestinal disease. Phenoximethyl penicillin was given by mouth throughout.

On the first day all patients received a single dose of 0.4 g (= 600,000 IU) penicillin V on an empty stomach. Blood samples for determination of penicillin concentration in the serum were collected immediately before and 1, 4 and 8 h after the administration of penicillin. From the 2nd to the 5th day the patients were given oxyphenbutazone (Tanderil®) 0.6 g in 3 daily doses, each of 0.2 g, equally divided over 24 h. On the 5th day they received a new single oral dose of 0.4 g penicillin V. The concentration of penicillin was checked in the same way as on the 1st day.

All blood samples were kept in a refrigerator (+4°) until the last sample of the day had been collected and they were then sent to the laboratory. The serum was then separated and frozen until both series of samples from each patient could be examined at the same time. The determinations were made using the cup-plate method according to GROVE and RANDALL[9], with *Sarcina lutea* (ATCC 9341) as test organism. Dilutions were, however, made with human normal serum instead of bovine albumen solution.

Results. The results are given in the Table. During treatment with oxyphenbutazone the serum concentrations were on an average twice as high as without oxyphenbutazone. The tendency was the same throughout, but the difference was significant ($p < 0.05$) only for determinations made 1 h after the administration. Because of widely diverging values after 4 h, the average increase from 0.11 to 0.25 μg/ml was not statistically significant.

Result and discussion. The results confirm LEGLER's and BRACHARZ' observation that a combination of oxyphenbutazone and penicillin V by mouth results in an increased serum penicillin concentration. These higher concentrations might result in a better penetration to the infected tissue, especially in poorly perfused areas.

This may be of practical importance in the treatment of bacterial infections in such cavities as the middle ear and paranasal sinuses or in foci with a tendency to be encapsulated. The local inhibitory effect of oxyphenbutazone on inflammation should presumably also counteract local oedema and therefore increase the diffusion into inflamed tissues. In this connection it should be borne in mind that oxyphenbutazone does not influence phagocytosis or antibody formation[10–12].

As for the absence of significantly increased penicillin concentrations 4 h after oral administration of penicillin, which was also observed by LEGLER and BRACHARZ, there is a certain parallellism with the previously known change of the distribution of sulphonamides as a result of the action of other drugs[13]. Among drugs studied in this respect and shown to be effective not only by active displacement but also by increasing the penetration of free sulpha to the tissues are sulphinpyrazone (Anturan®), phenylbutazone (Butazolidin®) and the main metabolite of the latter, oxyphenbutazone (Tanderil®). ANTON[13] in experiments in vivo demonstrated that these drugs produce a rapid fall of the sulphonamide concentration in the plasma by distribution out into the tissues.

Serum concentration of penicillin (IU/ml) without and with treatment with oxyphenbutazone

		Without oxyphenbutazone				With oxyphenbutazone			
		Before intake	1 h after	4 h after	8 h after	Before intake	1 h after	4 h after	8 h after
Pat. No.	1	—	0.98	0.14	—	—	2.40	0.20	—
	2	—	1.35	0.09	—	—	1.83	0.13	—
	3	—	0.42	0.27	—	—	1.32	0.20	—
	4	—	0.40	0.06	—	—	0.84	0.08	—
	5	—	0.34	0.05	—	—	0.42	0.17	—
	6	—	0.23	0.05	—	—	0.48	0.11	—
	7	—	0.69	0.16	—	—	1.05	0.11	—
	8	—	0.96	0.09	—	—	0.30	0.15	—
	9	—	0.22	0.15	—	—	1.85	0.06	—
	10	—	1.30	0.05	—	—	1.60	0.81	0.05
	11	—	0.75	0.10	—	—	1.45	0.19	—
	12	—	0.15	0.12	—	—	0.05	0.90	—
	13	—	0.84	—	—	—	0.84	—	—
	14	—	0.07	0.13	—	—	0.15	0.43	—
Average		—	0.62	0.11	—	—	1.04	0.35	—

—, denotes a serum concentration < 0.05.

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