cortex, parallel with the appearance of withdrawal signs. We also tried to produce physical dependence by giving increasing concentration of ethanol (2.5–17 g/kg daily) in the drinking water over a period of 8 weeks. But, these rats did not show apparent withdrawal signs. Moreover, the taurine concentration in their cerebral cortex did not change, though they showed slightly decreased levels of taurine in the brain stem and cerebellum. These findings suggest that taurine in the cerebral cortex may be involved in development of ethanol dependence or the appearance of withdrawal signs. Administration of taurine (0.6 g/kg, p.o., daily during ethanol administration) did not affect withdrawal signs of ethanol-dependent rats. It is unlikely that this negative result was due to poor incorporation of injected taurine into the brain, since taurine administration prevented decrease in the taurine concentration of ethanol-dependent rats (data not shown). Thus, it is still uncertain how changes in brain taurine are related to the appearance of withdrawal signs.

Table 2 shows the effect of taurine on the ethanol-induced sleeping time. In contrast to previous reports[8,9], taurine did not affect the sleeping time in either *JCL/ICR* or *dd* strain mice. We used 2 different strains, because it is well known that there are strain differences in the hypnotic action of ethanol[16,17]. Iida and Hikichi[8] first reported the antagonistic effect of taurine on the ethanol-induced sleeping time in *dd* mice. This effect was also observed by Boggan et al.[9] in C57BL/6J mice. But it is unlikely that the injected taurine entered the brain in these experiments, since exogeous taurine is incorporated into the brain only very slowly[18–21]. We observed that the taurine concentration in the brain was not changed by taurine administration under the same experimental conditions. Furthermore, we found that administration of taurine did not affect the ethanol concentration in the blood or brain of ethanol-treated mice (data not shown), indicating that taurine administration does not affect the metabolism of ethanol. Thus, at present, we cannot explain why our results differ from those of previous authors.

The present findings suggest that in the brain taurine, like some other putative neurotransmitters[23], is involved in the effect of chronic, but not acute, ethanol administration.

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Effects of probenecid on plasma/tissue distribution of ^{14}C-benzylpenicillin in rats

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Summary. Probenecid (50 mg·kg^{-1}) was found to induce an increase of the plasma concentration of ^{14}C-benzylpenicillin with a decrease of the concentration in liver and kidney. Accumulation in corresponding tissue slices was reduced by probenecid. Therefore, the well known increase of penicillin in plasma after probenecid seems to be not only due to an inhibition of renal excretion but also to a reduced tissue uptake in liver and kidney.

Probenecid, long known as an inhibitor of the tubular transport of weak organic anions[1–3], was widely used in therapy with penicillin to yield higher plasma levels. Numerous reports on the efficacy of this therapy and on probenecid combination with other antibiotics are present[4–6]. Today, at least in the case of certain strains of gonococci which are relatively resistent to penicillin G, ampicillin or amoxycillin, the combination with probenecid is indicated[7]. Nevertheless, the interactions of probenecid and penicillin are not completely understood. In some experimental studies extrarenal effects of probenecid have been demonstrated[8,9] but there is no reference to penicillin concentration in the tissue after probenecid. Therefore we studied in vitro and in vivo the plasma/tissue distribution of ^{14}C-benzylpenicillin under the influence of probenecid.

Methods. Male albino rats (NMRI - Hannover) weighing 360±60 g obtained 25 mg equivalent to 41,700 IE ^{14}C-benzylpenicillin/kg b.wt i.p. The labelled (Amersham Corp.) and the non-labelled benzylpenicillin (pharmacy, AK Rissen) were mixed to yield an appropriate sp. act. of

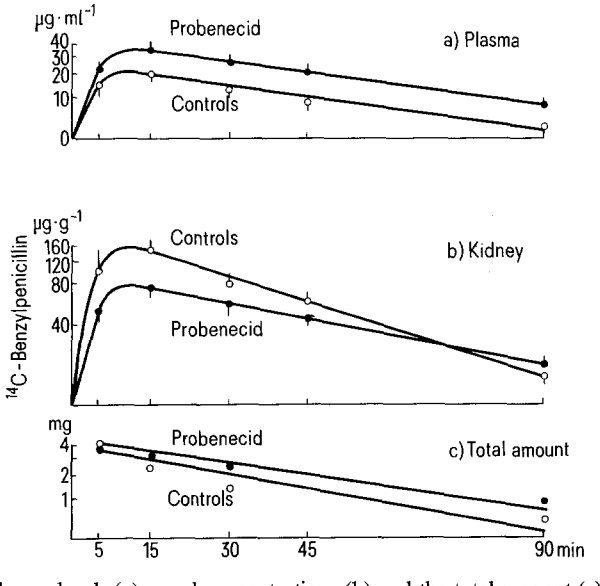
Content of benzylpenicillin in the tissue of rats

Probenecid ($mg \cdot kg^{-1}$)	Plasma ($\mu g \cdot ml^{-1}$)	Liquor ($\mu g \cdot ml^{-1}$)	lq/p ratio	Liver ($\mu g \cdot ml^{-1}$)	l/p ratio	Kidney ($\mu g \cdot ml^{-1}$)	k/p ratio	Skeletal muscle ($\mu g \cdot ml^{-1}$)	m/p ratio	N
0	20.3±1.0	1.3±0.5	0.066	139.8±16.7	6.9	143.0±20.0	7.0	4.8±1.0	0.24	6
10	18.8±1.7	1.4±0.3	0.073	104.3± 8.0*	5.5	94.3±11*	5.0	4.1±0.1	0.22	6
50	35.1±5.8*	2.0±0.8	0.057	100.0±17.8*	2.8	76.0±14.9*	2.2	6.1±0.8	0.17	6
100	39.6±3.5*	2.1±0.7	0.054	95.8±14.2*	2.4	61.8± 7.6*	1.6	5.6±0.9	0.14	6
200	46.7±4.5*	2.4±1.1	0.051	73.1±10.3*	1.6	76.9±10.3	1.6	5.8±0.6	0.13	5

Concentration of ^{14}C-benzylpenicillin in plasma and tissue of the rat as well as the calculated tissue/plasma ratios 15 min after i.p. application of 25 $mg \cdot kg^{-1}$ in controls and under increased doses of probenecid. N = number of experiments: results are given as the mean ± SD; * indicates significant difference from control values according to Student's t-test. $p < 0.01$.

0.7–2.0 $\mu Ci \cdot mg^{-1}$. Probenecid (Sharp and Dohme, München) was applicated i.p. 30 min before the experiments. 5, 15, 30, 45, and 90 min after administration of ^{14}C-benzylpenicillin the rats were killed and the radioactivity was measured in samples of plasma and cerebrospinal fluid (0.1 ml) and liver, kidney and skeletal muscle (200–300 mg), after combusting by a Tricarb Sample Oxidizer 305, by liquid scintillation counting. The radioactivity measured was related to the dose of benzylpenicillin and expressed as µg/g wet wt or per ml fluid.

Tissue slices 0.5 mm thick from rat liver and kidney prepared by a Stadie-Riggs microtome were incubated up to 180 min in carbogen-saturated Krebs-Ringer-Solution (mM: NaCl 136.0, KCl 2.67, $CaCl_2$ 1.8, $NaHCO_3$ 11.9, KH_2PO_4 0.417, $MgCl_2$ 0.507, glucose 5.0) at 37 °C and pH 7.4. The concentration of ^{14}C-benzylpenicillin and probenecid in the medium was 25 $\mu g \cdot ml^{-1}$ and 1.0 $mg \cdot ml^{-1}$ resp. The tissue/medium ratios (T/M) were calculated as described above from the radioactivity measured in medium and tissue.



Plasma levels (a), renal concentrations (b) and the total amount (c) of ^{14}C-benzylpenicillin in rats of controls (○——○) and under probenecid (●——●, 50 $mg \cdot kg^{-1}$ b.wt given 30 min before the beginning of experiments i.p.) 5, 15, 30, 45 and 90 min after i.p. application of 25 $mg \cdot kg^{-1}$ ^{14}C-benzylpenicillin. Results are given as the mean ± SD of 5 to 8 experiments. The radioactivity measured was related to the dose of benzylpenicillin given.

Results. It is shown in the figure, a, that under probenecid the concentration of benzylpenicillin was increased in the rat plasma whereas the half life (29.8 min) calculated was not different from controls (29.0 min). In contrast, the corresponding concentration in the kidney was decreased due to probenecid (figure, b) and the same holds true for the liver content. No significant effects of probenecid could be demonstrated in the cerebrospinal fluid (CSF) and skeletal muscle as shown in the table summarizing the results obtained 15 min after application of penicillin. The total amount of benzylpenicillin in the rat calculated from the weight of the organs and the corresponding concentrations is depicted in the figure, c. Under probenecid the half time of total elimination increased from 24.9 in controls to 33.2 min.

In liver and kidney slices benzylpenicillin accumulated up to a T/M ratio of 2.72 + 0.42 and 2.91 + 0.37 resp. and was reduced by probenecid (1 $mg \cdot ml^{-1}$) to values of 1.43 + 0.19 and 1.35 + 0.17 resp.

Discussion. The results presented let us assume that – according to previous reports[4,10] – besides the long-known inhibition of the tubular transport of penicillin, extrarenal effects of probenecid are also found. Indeed probenecid proved to inhibit the accumulation of benzylpenicillin in liver and kidney slices. Moreover, decreased levels in these organs were measured in vivo after probenecid application. Therefore the increase of plasma penicillin by probenecid might be the result of decreased tissue uptake.

Similar probenecid-induced changes in distribution have been reported in kinetic studies with ouabain[11]. In the same report it could be demonstrated that this effect was independent of biliary and renal excretion. From further experiments (not depicted) we conclude that this holds true in rats with ligated ductus choledochus and renal penduncles.

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