output in gastric fistula rats (Figure). The inhibition was apparent already during the first h after the injection and lasted for at least 4 h. After 2 injections of DGL the histidine decarboxylase activity and serum gastrin level were significantly increased in normal but not in antrectomized rats (Table). Our results confirm those of ANDERSSON et al.[2], in that DGL inhibits gastric acid secretion in the rat. However, inhibition was observed with a lower dose than reported by ANDERSSON et al.[2] (300–350 mg/kg) in their studies on 24-h pylorus-ligated rats. It thus seems probable that inhibition of acid secretion contributes to the ulcerprotective action of DGL. The mechanism, by which DGL inhibits acid secretion, is unknown. The present results clearly indicate that the inhibition is not due to suppressed gastrin release or to inactivation of histidine decarboxylase. It seems more probable that DGL exerts a direct inhibitory effect on the parietal cell. Treatments – surgical (vagotomy) or pharmacological (atropine, 'antigastrin') – inhibiting gastric acid secretion have previously been shown to increase histidine decarboxylase activity in normal but not in antrectomized rats[11]. Since endogenous gastrin plays an important role in the regulation of histidine decarboxylase activity[9], the increased enzyme activity may be explained by increased release of endogenous gastrin, due to the elevated antral pH. The present finding of an increased serum gastrin level after DGL strongly supports this hypothesis[12].

Histidine decarboxylase activity (HDA) and serum gastrin level in normal rats treated with saline or deglycyrrhizinized liquorice (DGL) and in antrectomized rats treated with DGL

Treatment	HDA (pmoles CO_2/mg/h)	Gastrin (pg eqv SHG/ml)
Normal, saline	5.2 ± 2.3 (7)	37 ± 3 (5)
Normal, DGL	18.4 ± 3.8 (12)[b]	122 ± 30 (5)[a]
Antrectomy, DGL	4.6 ± 1.2 (8)	27 ± 6 (5)

Means ± SEM(n). [a] $0.05 > P > 0.01$ and [b] $0.01 > P > 0.001$; Student's t-test.

Zusammenfassung. Nachweis, dass die Behandlung mit einem deglycyrrhizinierten Lakrizpräparat die basale Säurereaktion bei Ratten hemmt. Erhöhtes antrales pH führt zu vermehrter Freisetzung von antralem Gastrin mit bedeutender Aktivierung der Histidindecarboxylase in der Magenschleimhaut.

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[9] R. HÅKANSON and G. LIEDBERG, Eur. J. Pharmac. *12*, 94 (1970).
[10] R. HÅKANSON and G. LIEDBERG, Eur. J. Pharmac. *16*, 78 (1971).
[11] R. HÅKANSON and G. LIEDBERG, Experientia *27*, 1045 (1971).
[12] Acknowledgments: This study was supported by the Swedish Medical Research Council No. B73-04x-1007-08 and by the Albert Påhlsson Foundation.

Effect of Chronic Treatment with Mescaline upon Tissue Levels of the Drug

Development of tolerance to both the autonomic and subjective effects of mescaline in man was first reported by BALESTRIERI and FONTANARI[1] and later confirmed by WOLBACH et al.[2]. In the rat, tolerance to mescaline has been observed by a number of workers using a variety of schedules of reinforcement[3–7]. Although the fact of tolerance to mescaline is well established, the mechanisms by which this tolerance develops are unknown.

The observation in a behavioral test that prior exposure to a drug produces decreased responsiveness to that drug may be explained in several ways. In general, the possible mechanisms include 1. metabolic tolerance, an alteration in absorption, metabolism or excretion which reduces the concentration of drug at the target tissues, 2. cellular tolerance, a diminished sensitivity of the target tissue, and 3. behavioral tolerance, changes which arise via compensatory behavioral mechanisms. The present investigation examined the effects of repieated adminstration of mescaline upon the levels of the drug in brain and liver and in this way sought to determine the role, if any, of altered tissue concentrations in the development of rolerance to mescaline.

Materials and methods. Female rats of CFN strain (Carworth Farms) weighing 120–130 g were used to determine the effect of pretreatment with mescaline (40 mg/kg; i.p.) on tissue levels of mescaline. Mescaline hydrochloride was dissolved in 0.9% sodium chloride solution. The dose of mescaline is in terms of the free base. The test group (chronic) was injected with drug and the control group (acute) received saline for 2 days. On the third day both groups received mescaline. Rats were killed at various time intervals after the last injection and the concentration of mescaline in liver and brain was determined. In an experiment designed to assess the effect of the blockade of monoamineoxidase (MAO) on the development of tolerance to mescaline, 3 groups of rats were used. Groups II and III were treated with pargyline HCl on days 1 through 4 (day 1: 75 mg/kg: days 2–4: 25 mg/kg). In addition, group III received mescaline (40 mg/kg) on days 3 and 4. Finally, all groups were injected with mescaline (40 mg/kg) on day 5 and the level of mescaline in the liver was determined 30 min later.

[1] A. BALESTRIERI and D. FONTANARI, Archs gen. Psychiat. *1*, 279 (1959).
[2] A. B. WOLBACH, H. ISBELL and E. J. MINER, Psychopharmacologia *3*, 1 (1962).
[3] D. X. FREEDMAN, G. K. AGHAJANIAN, E. M. ORNIT and B. S. ROSNER, Science *127*, 1173 (1958).
[4] D. X. FREEDMAN, J. B. APPEL, F. R. HARTMEN and M. E. MOLLIVER, J. Pharmac. exp. Ther. *143*, 309 (1964).
[5] J. R. SMYTHIES, E. A. SYKES and C. P. Lord, Psychopharmacologia *9*, 434 (1966).
[6] E. A. CARLINI, M. T. A. SILVA, L. C. CESARE and R. M. ENDO, Med. Pharmac. exp. *17*, 534 (1967).
[7] H. A. TILSON and S. B. SPARBER, Psychopharmacologia *19*, 313 (1971).

Content of mescaline in brain and liver was determined by the methods of COHEN and VOGEL[8]. Tissue (whole brain or liver) was homogenized in a chilled Waring blender with 10 ml of distilled water. The homogenate was shaken for 20 min with 25 ml of toluene in the presence of 5 ml of 1 *N* NaOH and 3 g of NaCl. After centrifugation for 30 min, 20 ml of organic phase was extracted in 2 ml of 0.5 *M* boric acid by shaking for 10 min. Centrifugation for 20 min resulted in separation of the aqueous and organic phases. 1 ml of the boric acid extract was combined with 1 ml of 0.1 *M* borax solution and 0.2 ml of dansyl chloride (1 mg/ml in acetone) and was heated for 15 min in boiling water. After cooling for 3 min in ice cold water, the samples were shaken with 1.5 ml of chloroform for 5 min and then centrifuged for 10 min. The organic phase was read in a Farrand Ratio Fluorometer at 515 nm after activation of 365 nm. Tissue blanks and standards were always run along with the test samples. Concentrations of mescaline were expressed as µg per gram of tissue.

Effect of pretreatment with pargyline HCl on the amount of mescaline in the livers of rats treated acutely or chronically with mescaline (40 mg/kg)

Group	*n*	Pretreatment	Treatment	Liver mescaline [µg/g]
I	12	None	mescaline	21.8
II	12	pargyline	mescaline	54.9
III	12	pargyline + mescaline	mescaline	36.2

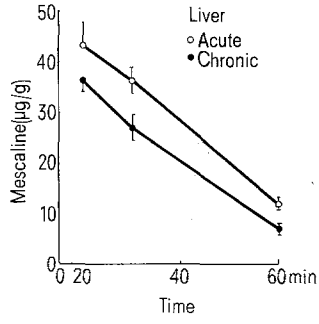

Fig. 1. Effect of acute and chronic treatment with mescaline, 40 mg/kg, on the concentration of mescaline in rat liver. Vertical lines indicate + S.E.

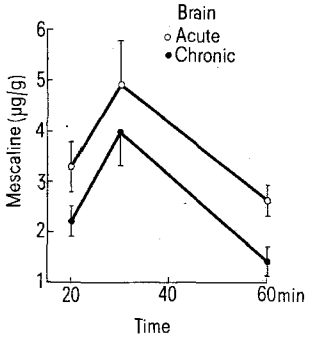

Fig. 2. Effect of acute and chronic treatment with mescaline, 40 mg/kg, on the concentration of mescaline in rat brain. Vertical lines indicate ± S.E.

Results and discussion. Figures 1 and 2 show the concentration of mescaline in liver and brain at various times after a fixed dose (40 mg/kg) of mescaline. The concentration of mescaline in liver and brain was lower in chronically trated rats as compared with acutely treated rats at all time intervals. In both tissues, the differences were statistically significant as determined by factorial analysis of variance (liver: $F = 11.62$; DF 1, 48; $p < 0.01$; brain: $F = 5{,}02$, DF 1.48; $p < 0.01$).

The metabolism of mescaline-^{14}C in the rat was studied by MUSACCHIO and GOLDSTEIN[9]. They could account for 94% of an i.p.-administered dose of the drug in the urine in terms of unchanged mescaline and its deaminated and N-acetylated metabolites. The product of deamination, 3,4,5-trimethoxyphenylacetic acid (TMPA), represented 42% of the total. If the decreased level of mescaline in rats treated chronically with mescaline is a consequence of enhanced activity of MAO, the difference between chronically and acutely treated rats should be absent or diminished when the enzyme is substantially inhibited. Inhibition of monoamineoxidase by pretreatment with pargyline significantly ($p < 0.01$) increased the levels of mescaline in liver (Table). However, a comparison of group II and group III indicates that the effect of chronic treatment with mescaline is not abolished by concurrent administration of pargyline. These data suggest that MAO or other amine oxidases which may be inhibited by pargyline do not play a major role in the observed changes in tissue levels.

Zusammenfassung. Bei chronisch behandelten Ratten war die Mescalin-Konzentration in Gehirn und Leber niedriger als bei akut behandelten Tieren. Die Hemmung der Monoaminooxydase durch Vorbehandlung mit Pargylin erhöhte signifikant die Mescalinmenge in der Leber. Ferner liessen die Untersuchungen den Schluss zu, dass die MAO oder andere Aminooxydasen, die durch Pargylin gehemmt werden, nicht die Hauptrolle bei den beobachteten Veränderungen in den Gewebekonzentrationen spielen.

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[8] I. COHEN and W. H. VOGEL, Experientia *26*, 1231 (1970).

[9] J. M. MUSACCHIO and M. GOLDSTEIN, Biochem. Pharmac. *16*, 963 (1967).

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