preparations (Figure, B), IPN would block the incorporation of the labelled amine in the storage vesicles and the total amount of H^3NE in the tissue would consequently be decreased in comparison with their controls.

The results obtained in the present paper confirm the hypothesis that IPN blocks the incorporation of H^3NE into storage vesicles present in the nerve endings.

Resumen. La incorporación de H^3NE a la auricula aislada de cobayo reserpinizado, tratado con Iproniazida (IPN) y atmosfera de Nitrogeno, es superior a la de sus controles sin IPN. En auriculas no reserpinizadas, la IPN aparece como agente bloqueante de la incorporación. Se sugiere que este bloqueo ocurre a nivel de las vesiculas especificas de almacenamiento presentes en las terminaciones nerviosas adrenergicas.

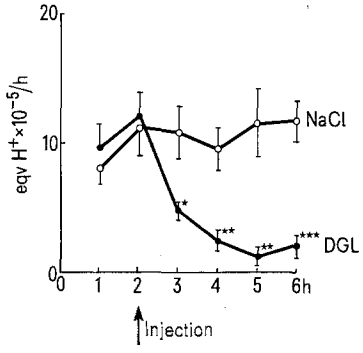
R. MARTINEZ-SIERRA, A. VELASCO-MARTIN and P. D. GARCIA DE JALON

Departamento de Farmacologia, Facultad de Medicina, Ciudad Universitaria, Madrid 3 (Spain),
24 November 1972.

Effect of Deglycyrrhizinized Liquorice on Gastric Acid Secretion, Histidine Decarboxylase Activity and Serum Gastrin Level in the Rat

Liquorice has been claimed to promote the healing of gastric ulcers in man. However, serious side effects such as water retention, electrolyte imbalance and hypertension preclude liquorice from wider clinical use. The component in liquorice responsible for its mineral corticosteroidlike activity has been identified as glycyrrhizinic acid. A deglycyrrhizinized liquorice preparation (DGL) has been reported to retain the ability to accelerate the rate of healing of gastric ulcers in man[1] and to protect pylorus-ligated rats from ulcer formation[2]. The mechanism by which DGL prevents ulcer formation in Shay rats is unknown. ANDERSSON et al.[2] reported a decrease of the acid output in DGL-treated rats after a dose slightly higher than the one which reduced the number of ulcers formed. Since 24 h pylorus ligation seemed to be poorly suited for studies on the inhibitory effect of a single dose of DGL on acid output, we decided to repeat the experiments with rats carrying chronic gastric fistulas. In another group of rats, the effects on histidine decarboxylase (the histamine forming enzyme) in the gastric mucosa and on the concentration of immunoreactive gastrin in serum were studied.

Altogether 35 male Wistar rats weighing 150–250 g were used. Acid secretion was studied in 8 rats carrying chronic gastric fistulas[3]. The fistula rats were fasted for 24 h and then restrained in Bollman-type cages. The fistulas were opened and the stomachs rinsed with 0.9% saline until the return was clear. 10 ml 0.9% saline was given s.c. to replace fluid losses. After the fistula had been draining freely for 1 h, basal acid secretion was collected for two 1-h periods, after which DGL (kindly supplied by Dr S. ANDERSSON, Dept. of Pharmacology, Karolinska Inst., Stockholm) 200 mg/kg, suspended in 0.9% saline 40 mg/ml, was given i.p., and 4 further 1-h portions obtained. Acid output was determined by titration with 0.02*N* NaOH, using phenolphtalein as indicator. The same animals received the same volume of 0.9% saline (i.p.) in a control experiment.



Effect of deglycyrrhizinized liquorice (DGL), 200 mg/kg i.p., on gastric acid output in 8 chronic gastric fistula rats. DGL or 0.9% saline given as indicated by the arrow. Mean ± SEM. * $0.05 > P > 0.01$; ** $0.01 > P > 0.001$ and *** $P < 0.001$ according to Student's *t*-test.

Before determination of histidine decarboxylase activity and gastrin in serum all rats were fasted for 48 h. 12 normal and 8 antrectomized rats[4], were given 200 mg/kg DGL i.p. twice with 3 h interval. 7 normal control rats received saline only. 3 h after the last injection the animals were lightly anaesthetized with ether, the abdomen opened and blood drawn directly from the caval vein. The blood was allowed to clot at room temperature and the serum was freeze-dried. The concentration of immunoreactive gastrin was determined radioimmunochemically using rabbit antibodies against human serum gastrin[5] and a monoiodinated gastrin preparation [6]. Gastrin concentrations were expressed as pg equivalent of synthetic human gastrin I (SHG) per ml serum. Previous studies showed that gastrin in rat serum was measured with an accuracy similar to that in human serum[7]. Immediately after exsanguination the stomach was removed, cut open along the greater curvature and rinsed in ice-cold saline. The mucosa of the oxyntic gland area was scraped off and homogenized in 0.1*M* phosphate buffer, pH 6.9, to a final concentration of 100 mg wet weight /ml. After centrifugation at 10,000 × *g* for 15 min at 0 °C, the histidine decarboxylase activity in the supernatant was determined by incubation with ^{14}C-carboxyl-labelled histidine[8]. The enzyme activity is expressed as pmoles CO_2 formed per mg mucosa and hour.

The i.p. injection of DGL in a dose of 200 mg/kg caused a marked and highly significant reduction of the acid

[1] A. G. G. TURPIE, J. RUNCIE and T. J. THOMSON, Gut *10*, 299 (1970).
[2] S. ANDERSSON, F. BÁRÁNY, J. L. F. CABOCLO and T. MIZUNE, Scand. J. GASTROENT *6*, 683 (1971).
[3] A. BEL, R. LEVRAT, J. NESMOS and R. GIRARD, J. med. Lyon, special issue, October 5 (1966).
[4] R. HÅKANSON and G. LIEDBERG, Eur. J. Pharmac. *18*, 31 (1972).
[5] J. F. REHFELD, F. STADIL and B. RUBIN, Scand. J. clin Lab. Invest. *30*, 221 (1972).
[6] F. STADIL and J. F. REHFELD, Scand. J. clin. Lab. Invest., *30*, 361, (1972).
[7] R. HÅKANSON, G. LIEDBERG, J. OSCARSON, J. F. REHFELD, F. STADIL and J. VANG, in press.
[8] R. HÅKANSON, Acta physiol, scand. suppl. *340* (1970).

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.

R. HÅKANSON, G. LIEDBERG, J. OSCARSON, J. F. REHFELD and F. STADIL

Departments of Pharmacology and Surgery, University of Lund, Kirurgiska Kliniken, Lasarettet, S-22185 Lund (Sweden); and Department of Clinical Chemistry, Bispebjerg Hospital and Department of Surgical Gastroenterology C, Rigshospitalet, Copenhagen (Denmark), 6 December 1972.

[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).