Potentiation of Histamine and Inhibition of Diamine Oxidase by Mescaline

Mescaline (see Figure 1A), a drug that can induce catatonia[1], has a similar chemical structure to the amine 3,4-dimethoxyphenylethylamine (Figure 1B) recently isolated from the urine of schizophrenic patients[2,3]. On the other hand, bulbocapnine (Figure 1C) is also a catatonic drug and has a 4-methoxyphenylethylamine moiety[4]. Furthermore, it has been demonstrated that bulbocapnine is able to potentiate histamine responses in biological preparations, probably because of its inhibitory action on diamine oxidase[5,6].

We therefore decided to investigate whether mescaline would be able to enhance histamine responses on two pharmacological preparations. Rats were anaesthetized with ethylurethane, 1.5 g/kg i.p. and the carotidean blood pressure was recorded on a smoked drum with a Condon's mercury manometer[7]. Drugs were injected through the iliac external vein. As seen in Figure 2, mescaline strongly potentiated the hypotensive response of histamine. In a series of 5 animals, we obtained an average potentiation of 104% (standard deviation = 61) of the histamine hypotension following the injection of 24 mg/kg of mescaline by intravenous route.

Histamine spasmogenic activity on the guinea-pig ileum was also enhanced by mescaline; in five experiments the addition of 10 to 20 μg of the alkaloid into a 10-ml chamber containing the gut, provoked an enhancement of 30 to 50% of the histamine responses.

The inhibitory effect of mescaline on the histaminolytic power of diamine oxidase is seen in Figure 3. About 96% of histamine was destroyed after 4 h of incubation with diamine oxidase, whereas a 90% protection of histamine was observed when mescaline was added to the incubation tube at a final concentration of $1 \cdot 10^{-5} M$, 3 h prior to the addition of histamine.

The fact that mescaline and bulbocapnine, both catatonic agents, have a common 4-methoxyphenylethylamine moiety which is also present in the 3,4-dimethoxyphenylethylamine isolated from the urine of schizophrenic patients, certainly deserves attention. Both alkaloids are inhibitors of histaminolysis, and 3,4-dimethoxyphenylethylamine has been described as a catatonic agent[1]. It is also relevant that schizophrenic patients have not only a higher plasmatic level of histamine[8,9] but also a relative

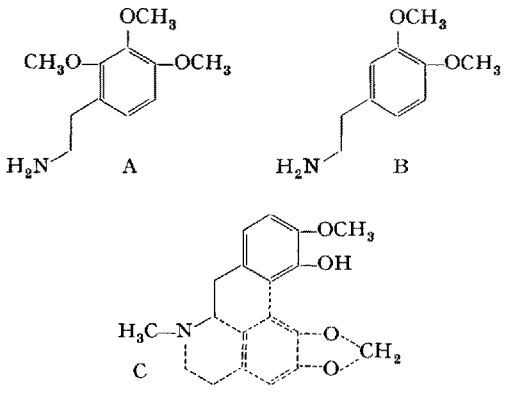

Fig. 1. The chemical structure of mescaline (A), 3,4-dimethoxyphenylethylamine (B) and bulbocapnine (C). The drugs have a 4-methoxyphenylethylamine moiety which is shown in solid lines.

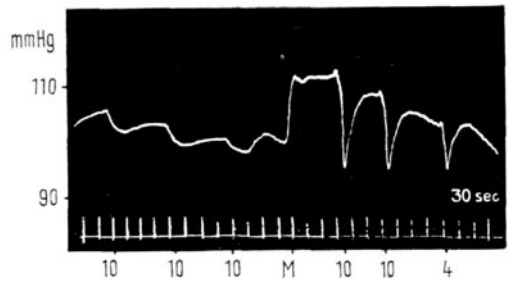

Fig. 2. Hypotensive effect of histamine on rat blood pressure before and after injection of mescaline. 240 g female rat, anaesthetized with 1.5 g/kg of ethyluretane i.p. Bottom numbers refer to μg of histamine injected into the external iliac vein. At M, 12 mg/kg of mescaline were injected by the same route.

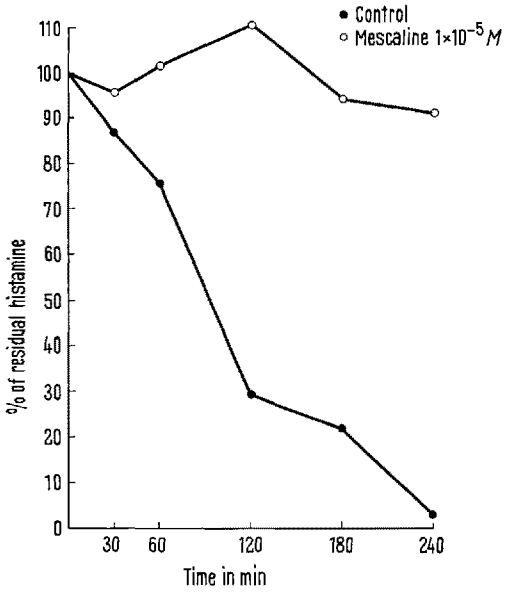

Fig. 3. The inhibitory activity of mescaline on diamine oxidase. 1 mg of hog kidney diamine oxidase (Nutritional Biochemical Corporation) and mescaline at a final concentration of $1 \cdot 10^{-5} M$ was preincubated for 3 h at 37°C with the pH adjusted to 7.0 with Sorensen's phosphate buffer. 30, 60, 120, 180, and 240 min after the addition of 3 μg of histamine (final volume in test tube = 10.0 ml), aliquots were taken and assayed for residual histamine activity on a guinea-pig ileum. Each point of the control curve represents the mean of 10 experiments, and the curve with mescaline was obtained from 4 experiments.

[1] A. M. ERNST, Acta physiol. pharmacol. neerl. *11*, 48 (1962).
[2] A. J. FRIEDHOFF and E. VAN WINKLE, J. nerv. ment. Dis. *135*, 550 (1962).
[3] M. TAKESADA, Y. KAKIMOTO, I. SANO, and Z. KANEKO, Nature, Lond. *199*, 203 (1963).
[4] A. M. ERNST, Nature, Lond. *193*, 178 (1962).
[5] J. E. CHAPMAN and E. J. WALASZEK, Med. exp. *6*, 95 (1962).
[6] J. E. CHAPMAN and E. J. WALASZEK, Biochem. Pharmacol. *11*, 205 (1962).
[7] N. F. CONDON, Brit. J. Pharmacol. *6*, 19 (1951).
[8] L. DOUST, H. HUSDAN, and M. SALNA, Nature, Lond. *178*, 492 (1956).
[9] P. STERN, Arch. int. Pharmacodyn. *109*, 294 (1957).

insensitivity to histamine[10,11]. Histamine exists in the brain in a typical subcellular distribution[12,13].

Therefore, the possibility should be considered that experimental catatonia induced with pharmacological agents possessing the 4-methoxyphenylethylamine moiety, and the catatonic state often observed in human schizophrenics, could be at least in part related to a disturbance of histamine catabolism in the brain.

Zusammenfassung. Anhand zweier Versuchsanordnungen wird gezeigt, dass Meskalin Histaminwirkungen verstärken kann. Ausserdem vermag es die Histamin zerstörende Wirkung der Diaminooxydase zu hemmen (in 10^{-5}-molarer Konzentration).

Es wird die Möglichkeit diskutiert, dass diese Eigenschaften mit der 4-Methoxyphenyl-äthylamin-Struktur des Meskalins in Zusammenhang stehen könnten.

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Secção de Fisiologia Animal, Instituto Biológico, São Paulo (Brazil), July 29, 1964.

[10] J. Leblanc and L. Lemieux, Med. exp. *4*, 214 (1961).
[11] T. E. Weckowics and R. Hall, J. nerv. ment. Dis. *125*, 452 (1957).
[12] E. A. Carlini and J. P. Green, Brit. J. Pharmacol. *20*, 264 (1963).
[13] E. A. Carlini and J. P. Green, Biochem. Pharmacol. *12*, 1448 (1963).

Testicular Degeneration after *l*-Tyrosine Feeding in Rats, Role of Ascorbic Acid

Toxicity due to high level of tyrosine feeding in rats has been observed by many investigators[1,2]. Hueper and Martin[3] have noted epithelial atrophy and formation of giant spermatid cells in testes during tyrosine toxicosis. Spermatogenic arrest has been observed in ascorbic acid deficient animals[4]. Ghosh and Guha[5] have recently reported inhibition of ascorbic acid biosynthesis in rats fed a high dose of tyrosine. Administration of vitamin C has been found to correct the defective metabolism of tyrosine in infants fed a high protein diet[6]. In the present investigation, the role of ascorbic acid on the testicular degeneration in rats maintained on a high dietary intake of *l*-tyrosine is presented.

Sixteen healthy male rats weighing 65 to 70 g were selected for the experiment. They were offered a standard laboratory diet for a few days prior to experimentation. All the rats then received a diet containing 5% each of *l*-tyrosine and sucrose along with their basal diet for 5 weeks. The animals were then divided into two groups of equal number. Eight in the experimental and the remaining rats in the control group. The experimental group of tyrosine-fed animals were treated with ascorbic acid by the intramuscular route at a dose level of 1 g/kg body weight per animal per day for one week, and the control group received tyrosine only as in the preceding weeks. All the animals were sacrificed by cerebral concussion after six weeks of treatment. Testes of the animals were carefully removed and fixed in carnoy. Paraffin sections were stained with hematoxylin and eosin for histological study.

Histologically, a marked atrophy of the testes has been observed in the rats fed a high dose of tyrosine. The lamina propria (Tunica albuginia) of the testes was found

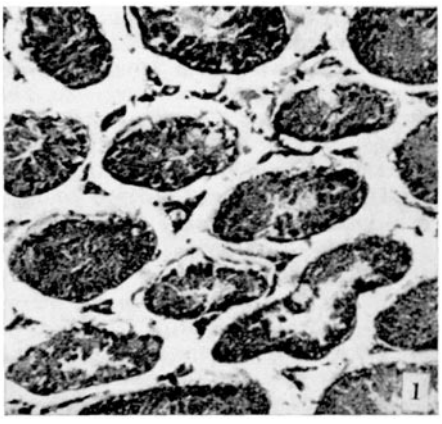

Fig. 1. Testis from *l*-tyrosine-fed rat, showing complete inhibition of spermatogenesis (× 96).

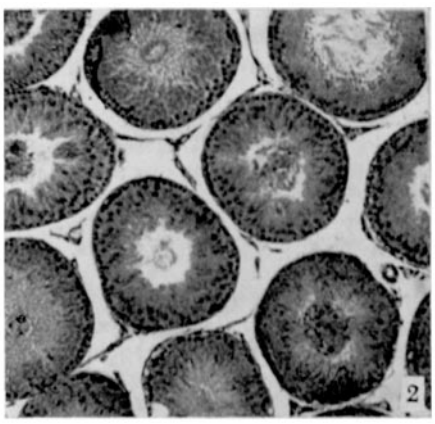

Fig. 2. Testis from *l*-tyrosine-fed rat treated with ascorbic acid. Normal spermatogenesis can be noted. Compare with Figure 1 (× 96).

[1] D. A. Benton, A. E. Harper, H. E. Spivey, and C. A. Elvehjem, Arch. Biochem. Biophys. *60*, 156 (1956).
[2] W. Schweizer, J. Physiol., Lond. *106*, 167 (1947).
[3] W. C. Hueper and G. J. Martin, Arch. Path. lab. Med. *35*, 685 (1943).
[4] B. P. Kocen and L. F. Cavaszos, Proc. Soc. exp. Biol. Med. *98*, 485 (1958).
[5] S. Ghosh and B. C. Guha, Biochem. biophys. Acta *89*, 440 (1963).
[6] S. Z. Levine, E. Marples, and H. H. Gordon, Science *90*, 620 (1939).