Zusammenfassung. Beiderseitige Exstirpation der Nebennieren vermindert die Toxizität von Neomycin und *d*-Tubocurarin.

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Blocking Action of Desmethylimipramine (DMI) on the Noradrenaline Depletion by Tyramine

There is increasing experimental evidence to support the concept that noradrenaline may be considered to exist in two physiological compartments, one of which can be promptly released by tyramine, while the other is more tightly bound[1–3].

It has been reported that imipramine, the methylated derivative of DMI, decreased the pressor response to tyramine in cats[4,5]. Recent work in this laboratory[6] showed that DMI also inhibited the pressor and positive chronotropic responses to tyramine in chloralized, vagotomized dogs. The present study was undertaken in an attempt to gain further insight into the mechanism by which DMI affects the response to tyramine.

The influence of DMI on noradrenaline content, and on the depletion induced by tyramine on rat's heart, was examined.

Material and methods. Unanaesthetized Wistar rats of either sex (140 to 210 g) were divided into four experimental groups. In each one, the animals received two successive injections of drugs 60 and 30 min prior to being sacrificed. In the first group (12 animals), only the solvent without DMI and 0.9% NaCl solution were given, respectively. The second group (15 animals) received the solvent and tyramine (15 mg/kg). To the third group (15 animals) DMI (20 mg/kg) and a 0.9% NaCl solution were administered. The last group (11 animals) was injected with both DMI and tyramine in the same doses as before. DMI and the solvent of DMI were given intraperitoneally, tyramine and NaCl 0.9% intramuscularly. Rats were sacrificed by a blow on the head and the hearts rapidly removed for analysis of catecholamine content. The tissues were homogenized in 5% trichloroacetic acid and the catecholamines extracted according to the method of von Euler and Lishajko[7]. The fluorometric determinations were performed as described by Cohen and Goldenberg[8], by means of a Farrand fluorometer. Only data concerning the content of noradrenaline will be reported here. Data were not corrected for an average recovery of 90%. DMI was prepared as a stock solution of the following composition: N-(-γ-methylamino-propyl-imino-dibenzyl-)-HCl (DMI), 1.25 g; glycerine, 2.0 g; sodium ascorbate, 0.11 g; cysteine HCl, 0.1 g; distilled water up to 100.0 ml. Tyramine was dissolved in 0.9% NaCl solution and used as the hydrochloride.

Results and discussion. The data in the Table show that DMI significantly prevents the tyramine-induced depletion of noradrenaline.

Therefore there is good agreement between the biochemical evidence of the impaired depletion of noradrenaline and the absence of pharmacological adrenergic responses to tyramine after DMI.

In a previous work, we found in the chloralized dog that guanethidine (12 mg/kg) displaced the pressor dose-response of tyramine to the right, whereas DMI (3 mg/kg) abolished almost completely the responses to all doses of tyramine employed[6]. On the other side, using a similar procedure to that described in this paper, Bhagat showed that guanethidine did not antagonize the tyramine-induced depletion of noradrenaline[9]. Thus, the blocking action of DMI on tyramine responses appears to be different from that of guanethidine. It was shown that cocaine blocked noradrenaline depletion by tyramine[10,11]. Since DMI antagonizes, like cocaine, the stimulatory effects of tyramine, it is possible that one drug resembles the other as concerns influence on tyramine responses.

The effect of tyramine 15 mg/kg and DMI 20 mg/kg upon the noradrenaline content of the rat's heart (μg/g of fresh tissue)[a]

I	Controls	0.457 ± 0.010
II[b]	Tyramine	0.202 ± 0.015
III	DMI	0.467 ± 0.035
IV	DMI + tyramine	0.437 ± 0.056

[a] Figures represent mean $\pm$ S.E. [b] 't' tests between group II and the other three groups, $p < 0.001$.

Zusammenfassung. Mit Desmethylimipramin vorbehandelte Ratten zeigen im Herzen keine Abnahme von Noradrenalin durch Tyramin. Daraus wird gefolgert, dass eine kokainähnliche Wirkung vorliegt: Desmethylimipramin und Kokain heben die pharmakologischen Wirkungen von Tyramin weitgehend auf.

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