($p < 0.05$) when compared with rats bearing ventromedial lesions (operated on day 24) but not when compared with rats operated somewhat later (Group 8). However, this decrease in food intake was not reflected in the body weight.

Placement of unilateral hypothalamic lesions in rats bearing regenerating adrenals (Groups 9 and 10), adrenal-enucleation in rats bearing unilateral ventromedial lesions (Groups 11 and 12) and placement of unilateral hypothalamic lesions alone (Groups 13 and 14) did not result in significant changes in food intake, either when compared within the unilateral groups (Group 9 through Group 14), or with controls (Groups 1 and 2) and rats with bilateral lesions and regenerating adrenals (Groups 3 to 6). However, rats with unilateral right lesions did show probably significant ($p < 0.05$) changes in food intake when compared with rats bearing bilateral ventromedial lesions (Groups 14 and pooled Groups 7 and 8 respectively).

HALASZ and SZENTAGOTHAI[11] have demonstrated that adrenalectomy resulted in swelling of cell nuclei of ventromedial neurons and that increased adrenal function, e.g. as under stress, lead to shrinkage of these cell nuclei. Furthermore, unilateral adrenalectomy resulted in swelling of cell nuclei in the contralateral ventromedial nucleus and shrinkage on the ipsilateral side. The authors suggested a nervous functional connection between the adrenal gland and the ventromedial nuclei, since interruption of the nervous connection between the adrenal and the celiac ganglion and the sympathetic chain induced exactly the same changes in nuclear size of the ventromedial nuclei as did adrenalectomy or adrenal cortical atrophy brought about by cortisone administration. They assumed that nervous information from the adrenal cortex, presumably from the capsular receptors described by KISS[13], must fairly directly reach the contralateral ventromedial nuclei. Further evidence for this concept came from the demonstration of a neurosecretory material in the ventromedial nuclei which could be shown after formol-pyridine fixation and Bielschowsky-Gross impregnation. This argyrophilic substance[12], which is very sparse in healthy cats and dogs, could be demonstrated in great abundance after adrenalectomy and following severe stress. This neurosecretory material is produced exactly at the anatomical site, the bilateral destruction of which brings about a significant decrease of adrenal weight. In our studies, too, decreased adrenal weight occurred in rats with ventromedial lesions. These and other findings will be reported elsewhere[14].

Our present findings suggest, however, that the influence of the adrenal gland on the ventromedial hypothalamic nucleus does not extend to the control of spontaneous food intake. The present results support the findings of KENNEDY[9] and BERNARDIS et al.[10], and BERNARDIS[18], that ventromedial lesions placed in weanling rats are not as hyperphagia-producing as when placed in adult rats. Very young, growing rats eat twice as much in relation to their body weight as do adults and release of the restraint on feeding behavior by placement of electrolytic lesions in the satiety center apparently cannot exceed the inherent hyperphagia of growth. These considerations might be cogently invoked in interpreting the lack of influence of the adrenal gland on food intake as shown in the present report[18].

Zusammenfassung. Die von HALASZ und SZENTAGOTHAI gezeigte funktionelle Beziehung der Nebennierenrinde mit dem N. ventromedialis hypothalami legte die Vermutung nahe, dass möglicherweise diese Kerne die Futteraufnahme kontrollieren und durch Nebennierenentkernung beeinflusst werden können. Nach unseren Ergebnissen bei jungen, weiblichen Ratten ist dies sicher nicht der Fall. Auch die erhöhte Futteraufnahme normaler Ratten, welche durch Läsionen in den ventromedialen Kernen hervorgerufen werden kann, blieb durch Enukleierung der Nebenniere unbeeinflusst.

L. L. BERNARDIS and F. R. SKELTON

Department of Pathology, State University of New York, Buffalo (New York USA), July 31, 1964.

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The Action of Epinephrectomy on the Toxicity of Neomycin

Under the framework of systematical research of neomycin, we have followed the action of epinephrectomy on its toxicity. The toxicity was tested in mice of a body weight of 16–18 g intravenously 24, 48 and 72 h following unilateral and bilateral epinephrectomy. The action of the epinephrectomy on the toxicity of neomycin has been compared with the action on the toxicity of other curareform substances, namely *d*-tubocurare and with a substance that, similarly to neomycin, lowers the ionized calcium in the blood, with ammonium oxalate and strychnine, the working mechanism of which differs thoroughly from that of curareform substances (central action)[1].

The toxicity in epinephrectomized mice has been acted upon by protamine, calcium chloride and hydrocortisone. The comparison was carried out by stating the toxicity of neomycin in normal mice with sham operation. Neomycin of 660 units/mg effectiveness (preparation Spofa, Czechoslovakia) was used. The results have been statistically evaluated by means of probit analysis, and a range of reliability of 95% probability has been established.

Results and discussion. We have found that bilateral epinephrectomy lowers the toxicity of neomycin, pro-

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Table I. The action of epinephrectomy on the toxicity of neomycin

Term after epinephrectomy	LD_{50} of neomycin in mg/kg (fiducial limits)	Toxicity of neomycin in %	Statistical significance	No. of animals
1) Control[a]	43.11 (38.73–46.42)	100		50
24 h	59.94 (53.52–66.62)	71	+	50
2) Control	43.55 (39.27–47.07)	100		50
48 h	49.66 (45.83–54.58)	87	—	50
3) Control	42.10 (37.87–45.42)	100		50
72 h	44.65 (41.08–47.63)	95	—	50
4) Control	45.62 (38.22–50.20)	100		25
24 h	57.10 (68.16–50.96)	79	+	25
24 h unilateral epinephrectomy	46.27 (40.77–56.81)	98	—	25

[a] Without epinephrectomy.

vided that the toxicity test is carried out 24 h following epinephrectomy; if the test is carried out 48 and 72 h after the operation, there is no result to be recorded (Table I).

Unilateral epinephrectomy did not affect the toxicity either (Table I). Similarly bilateral epinephrectomy decreases the toxicity of *d*-tubocurare, but has no effect on ammonium oxalate and strychnine (Table III). Protamine, which increases the toxicity of neomycin in normal mice, probably by bond to sulphomucopolysaccharides, has also annulled the decrease of toxicity of neomycin in epinephrectomized animals (Table II). Hydrocortisone and $CaCl_2$, decreasing the toxicity of neomycin in normal animals, have no further decreasing or increasing effect on the toxicity in epinephrectomized animals (Table II).

On the grounds of our results and their analysis, we assume that the toxicity decrease in neomycin and *d*-tubocurare is either due to a shift of the ions (Na^{1+}, K^{1+}, Ca^{2+}) or to the rise in the level of the acid sulphomucopolysaccharides in the blood, which would determine the acute toxicity of neomycin and of *d*-tubocurare as well.

Table II. Comparison of the effect of protamine, $CaCl_2$, and hydrocortisone on the toxicity of neomycin in normal and epinephrectomized animals

	Premedication in mg/kg	LD_{50} of neomycin in mg/kg (fiducial limits)	Toxicity of neomycin in %	Statistical significance	No. of animals
1)					
Without epinephrectomy	—	42.57 (28.20–51.09)	100	Control	25
Without epinephrectomy	Protamine 20[a]	33.90 (28.49–39.47)	126	+	25
Epinephrectomy 24 h	—	60.61 (50.28–87.66)	70	+	25
Epinephrectomy 24 h	Protamine 20	39.47 (26.42–78.33)	107	—	25
2)					
Without epinephrectomy	—	41.93 (37.64–45.57)	100	Control	50
Without epinephrectomy	$CaCl_2$ 100	61.69 (56.96–66.74)	68	+	50
Epinephrectomy 24 h	—	52.36 (43.84–58.54)	79	+	50
Epinephrectomy 24 h	$CaCl_2$ 100	62.89 (56.11–76.35)	66	+	50
Without epinephrectomy	Hydrocortisone[b] 2 × 10 mg	53.18 (46.14–60.17)	77	+	44
Epinephrectomy 24 h	Hydrocortisone 2 × 10 mg	52.52 (46.33–58.93)	79	+	53

[a] Protamine (preparation Spofa, Czechoslovakia) was administered intravenously 15 min before testing the toxicity. [b] Hydrocortisone (Solu, Cortef, England) was administered 10 mg/kg intraperitoneally 3 h before testing the toxicity and 1 h 10 mg/kg intravenously.

Table III. The action of epinephrectomy on the toxicity of *d*-tubocurare, ammonium oxalate and strychnine nitrate

Substance[b]	Period after epinephrectomy	LD_{50} of substances –/kg (fiducial limits)	Toxicity in %	Statistical significance	No. of animals
1)					
d-Tubocurare[c]	Control[a]	59 μg (46– 75)	100		50
d-Tubocurare	24 h	95 μg (84–126)	62	+	55
2)					
Ammonium oxalate	Control	83.98 mg (70.85–91.39)	100		45
Ammonium oxalate	24 h	93.59 mg (86.95–101.70)	90	—	50
3)					
Strychnine nitrate	Control	391.25 μg (311.25–475.00)	100		50
Strychnine nitrate	24 h	460.00 μg (361.25–552.50)	85	—	55

[a] Without epinephrectomy. [b] Intravenous administration. [c] Preparation Spofa, Czechoslovakia.

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

V. Sobek*, Z. Roth**, and Anna Kargerová*

*Research Laboratory of Pathology, Therapy and Prevention of Infectious Diseases of the Faculty of Children's Diseases**, *Prague-Bulovka and Institute of Industrial Hygiene and Occupational Diseases***, *Prague-Vinohrady (Czechoslovakia), July 9, 1964.*

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.

A. J. Kaumann and Nidia Basso

Centro de Investigaciones Cardiológicas, Facultad de Ciencias Médicas, Universidad de Buenos Aires (Argentine), August 24, 1964.

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