

THE EFFECT OF THE NEW GANGLION-BLOCKING SUBSTANCE TETRAMINE ON THE ORGANISM'S REACTIVITY TO INSULIN

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Thorough experimental investigation is required before any new chemiotherapeutic agent can be introduced into medical practice. For several years, our laboratory has been working in collaboration with the collective of the Latvian SSR Academy of Sciences' Institute of Organic Synthesis on the experimental study of certain aspects of the physiological effect produced by Tetramine, a new ganglion-blocking substance (tetramethylene-bis-N-methylpiperidine diiodide— $C_{16}H_{34}N_2I_2$) synthesized at the institute.

The purpose of this work was to investigate Tetramine's effect on reactivity to insulin.

METHODS

The experimental animals were healthy rabbits weighing 2-2.8 kg each, kept under uniform conditions and fed the usual vegetable diet. The experiments were performed on an empty stomach. Insulin was injected intramuscularly in a dose of 1 unit/kg. A subcutaneous injection of 1 mg/kg Tetramine was administered 30 minutes before the insulin injection. Blood was taken for examination from the marginal vein of the ear. The blood sugar content was determined according to Hagedorn and Jensen.

Ten control experiments were conducted first in order to determine the effect of a single Tetramine injection on the sugar content of the rabbits' blood. The blood of each animal was examined at several intervals over a period of two hours—15, 30, 60 and 120 minutes after the subcutaneous injection of the preparation. In the second, or main series of experiments, we determined the effect of Tetramine on the character of the hypoglycemia induced by intramuscular administration of insulin. To this end, we first determined each animal's hypoglycemic reaction to insulin and then, two to three days later, its reactivity to insulin on a background of the Tetramine injection.

RESULTS

The experiments showed that the subcutaneous injection of Tetramine did not, on the average, materially affect the blood sugar content (Table 1).

TABLE 1. Effect of Single Subcutaneous Injection of Tetramine on Blood Sugar Content
(Average Data from 10 Experiments)

Blood sugar content (in mg %)					Maximal change (in mg%)
before admin- istration of preparation	after administration of preparation				
	15 min	30 min	60 min	120 min	
114.8±3.13	130.4±4.14	130.2±6.10	122.3±4.84	115.4±3.81	+ 19

The intramuscular injection of insulin (in a dose of 1 unit/kg) caused a regular decrease in the blood sugar level of the experimental animals. The absolute levels of maximal change in the blood sugar content fluctuated from -38 to -92 mg % (Table 2).

In every case in which Tetramine was subcutaneously injected 30 minutes before the insulin injection, a sharper decrease in the blood sugar content was observed than in the experiments with insulin alone. The maximal changes in the blood sugar content in this experimental series fluctuated between -55 and -97 mg%. In a large number of cases, the blood sugar content reached acute hypoglycemic levels long before the end of the experiment (after 60-90 minutes). On a background of Tetramine, insulin induced hypoglycemic convulsions in 8 out of 12 rabbits, which were successfully arrested by the subcutaneous injection of adrenalin.

The data obtained allow the conclusion that Tetramine raises the sensitivity of a rabbit's body to insulin. The results of our investigations are in accord with the data concerning benzine, pachycarpine and tetraethylammonium iodide obtained by S. M. Leites and T. S. Yakusheva [2], who found that these substances increase the reactivity of dogs to insulin administered subcutaneously under conditions of alloxan diabetes, and with the data of I. A. Drzhevetskaya [1] as to the analogous effect of ganglerone [an anticonvulsant] and, particularly, pentamine [methyliminodiethylene-bis-ethyldimethylammonium bromide] and dicoline [1,6-dimethylpipercolinic acid diethylaminoethyl ester diiodomethylate].

TABLE 2. Effect of Tetramine on Rabbits' Reactivity to Insulin Administration

Rabbit no.	Substance administered	Blood sugar content (in mg%)					Maximal change (in mg%)
		original level	15 min	30 min	60 min	120 min	
1	Insulin (control)	122	-	108	49	30	-92
	Tetramine + insulin	120	93	48	45	23	-97
					(Hypoglycemic convulsions)		
2	Insulin (control)	96	75	41	49	53	-55
	Tetramine + insulin	127	82	57	(Hypoglycemic convulsions)		
3	Insulin (control)	116	82	65	37	50	-79
	Tetramine + insulin	138	93	48	(Hypoglycemic convulsions)		
4	Insulin (control)	87	80	51	40	38	-49
	Tetramine + insulin	88	71	56	45	32	-56
5	Insulin (control)	89	72	70	48	48	-41
	Tetramine + insulin	83	63	48	56	28	-55
6	Insulin (control)	83	74	50	44	29	-54
	Tetramine + insulin	97	51	43	46 (Hypoglycemic convulsions)		
7	Insulin (control)	82	63	45	47	35	-47
	Tetramine + insulin	80	72	40	32	20	-60
					(Hypoglycemic convulsions)		
8	Insulin (control)	82	57	35	39	35	-47
	Tetramine + insulin	90	68	30	28	34	-62
9	Insulin (control)	70	54	53	33	32	-38
	Tetramine + insulin	74	67	62	22 (Hypoglycemic convulsions)		
10	Insulin (control)	85	83	47	42	30	-55
	Tetramine + insulin	90	65	50	34	26	-64
11	Insulin (control)	103	97	74	57	49	-54
	Tetramine + insulin	85	45	41	31	23	-62
					(Hypoglycemic convulsions)		
12	Insulin (control)	97	91	53	59	70	-44
	Tetramine + insulin	90	75	60	37	25	-65
					(Hypoglycemic convulsions)		

These data concerning Tetramine's effect of increasing the organism's sensitivity to insulin are of practical interest in that they emphasize the need for extraordinary caution in prescribing both insulin and Tetramine to a patient at the same time (as in a combination of diabetes mellitus and hypertonic disease, diabetes and endarteritis, etc.). On a background of Tetramine administration, the usual therapeutic doses of insulin can cause undesirable, acute hypoglycemic symptoms. The physiological mechanism of this phenomenon will be the subject of later investigations.

SUMMARY

A study was made of the effect produced by Tetramine, a new ganglionblocking substance, synthesized at the Institute of Organic Synthesis of the Latvian SSR Academy of Sciences, on the character of hypoglycemia caused by intramuscular insulin administration. The results demonstrated that subcutaneous injection of Tetramine 30 minutes prior to insulin administration always leads to a more marked reduction of blood sugar level than with the administration of insulin alone. In a considerable number of cases the blood sugar level showed a marked drop prior to the end of experiment, with the occurrence of hypoglycemic convulsions. Thus, preliminary administration of Tetramine causes a more pronounced insulin action, i.e., Tetramine increases the rabbit's sensitivity to insulin. The data obtained may be of some practical interest, since it shows that particular care should be taken in simultaneous prescription of insulin for hypertensive disease, diabetes and endarteritis, etc. If given against the background of Tetramine action usually therapeutic doses of insulin may cause untoward sharp hypoglycemic phenomena.

LITERATURE CITED

1. I. A. Drzhevetskaya, Probl. Éndokrinol. i gormonoterap., 1, 8 (1959).
2. S. M. Leites and T. S. Yakusheva, Probl. Éndokrinol. i gormonoterap., 4, 41 (1955).

All abbreviations of periodicals in the above bibliography are letter-by-letter transliterations of the abbreviations as given in the original Russian journal. *Some or all of this periodical literature may well be available in English translation.* A complete list of the cover-to-cover English translations appears at the back of this issue.
