

ACTION OF SEROTONIN ON THE BLOOD SUGAR LEVEL AND INSULIN EFFECT

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Since the isolation of serotonin in a pure form [10], many researches have been published dealing with the study of this compound. At the present time considerable progress has been made in the study of the biosynthesis and metabolism of serotonin, its distribution in the organs and tissues, and its action on the animal organism. Several workers [2-5, 9] have investigated the biological role and physiological action of serotonin.

Interesting findings have been obtained showing that serotonin takes part in the transmission of nervous impulses and, in conjunction with acetylcholine, plays an important role in the regulation of various functions of the central nervous system.

Bearing in mind that the administration of serotonin leads to pathological symptoms related to the central nervous system, and also the fact that serotonin is the principal mediator of nervous impulses in the central division

TABLE 1. Effect of Subcutaneous and Intravenous Injection of Various Doses of Serotonin on the Blood Sugar Level in Rabbits

Date of in- vestigation (1962)	Weight of animal (in kg)	Dose of serotonin (in mg/kg)	Sugar level (in mg %)					
			sugar level (in mg%)	time after injection of serotonin				
				30 min	1 h	2 h	3 h	4 h
Subcutaneous injection								
2/II	2.7	2.0	104	100	93	88	84	81
5/II	2.1	2.0	88	109	116	103	98	116
15/III	2.5	2.0	68	68	73	61	70	70
18/III	2.3	2.0	75	78	80	79	88	18
20/III	2.4	2.0	93	101	110	90	94	95
3/II	2.3	5.0	115	109	122	120	111	91
6/III	2.7	5.0	130	118	118	109	94	84
7/III	2.0	5.0	96	91	98	95	105	89
15/III	2.5	5.0	96	93	110	87	90	89
Intravenous injection								
2/II	3.0	2.0	86	83	81	70	97	98
5/II	2.3	2.0	121	132	143	143	109	102
15/III	2.8	2.0	84	86	93	84	90	90
15/III	3.0	8.0	86	93	98	80	85	93
20/III	2.2	2.0	96	93	97	80	107	105
3/II	2.4	5.0	72	93	102	102	76	71
7/III	3.1	5.0	95	93	103	95	102	93
8/III	2.5	5.0	122	102	102	161	143	105
8/III	2.7	5.0	100	123	125	159	150	120
15/III	3.0	5.0	86	112	108	80	90	90

TABLE 2. Effect of Subcutaneous Injection of Various Doses of Serotonin on the Blood Sugar Level in Dogs

Date of investigation (1962)	Weight of animal (in kg)	Dose of serotonin (in mg/kg)	before injection	Sugar level (in mg %)				
				time after injection of serotonin				
				30 min	1 h	2 h	3 h	4 h
31/V	10,0	2,0	79	79	79	82	85	77
31/V	8,7	2,0	87	87	84	80	79	79
11/VI	18,0	2,0	67	68	79	83	93	93
18/VI	11,0	2,0	79	93	88	89	81	70
9/VII	8,0	2,0	75	84	79	75	73	64
4/VI	8,6	5,0	82	87	96	82	80	80
4/VI	11,4	5,0	67	68	78	78	77	85
9/VII	6,8	5,0	75	86	84	72	70	59
11/VII	9,0	5,0	69	73	77	107	105	105
18/VII	12,0	5,0	81	83	81	81	72	70

of the parasympathetic nervous system [8], the effect of serotonin has been studied on the blood glucose level and on the development of the nervous syndrome during insulin hypoglycemia. The starting point was the author's previous findings [1] relating to the significance of the blood glucose level in the process of development of the nervous disorders in animals receiving insulin. According to the investigations of several workers [6], serotonin lowers the glucose consumption of the brain and the oxygen absorption. The action of serotonin was accordingly studied on the insulin effect and on the development of the nervous manifestations in hyperinsulinism.

EXPERIMENTAL METHOD

Experiments were conducted on rabbits and dogs. In the first series of experiments the blood sugar level was determined in the animals before and at various intervals after administration of serotonin. In the second series of

TABLE 3. Effect of Insulin on Blood Sugar Level in Rabbits after Preliminary Injection of Serotonin

Date of investigation (1962)	Weight of animal (in kg)	Dose of serotonin (in mg/kg)	Dose of insulin (in units/kg)	Sugar level (in mg%)						Manifestations accompanying insulin hypoglycemia
				before injection of serotonin	30 min after injection of serotonin	time after injection of insulin				
						30 min	1 h	2 h	3 h	
15/III	2.3	2.0	2.0	87	90	75	70	58	60	No convulsions
3/IV	2.2	2.0	2.0	107	123	93	65	38	36	Convulsions after 3 h
4/IV	2.9	2.0	2.0	101	101	89	57	46	48	Convulsions after 2-1/2 h
10/IV	3.1	2.0	2.0	98	105	78	70	60	56	No convulsions
16/IV	2.5	2.0	2.0	98	100	85	70	65	65	No convulsions
2/IV	2.7	5.0	2.0	97	98	81	67	49	47	No convulsions
3/IV	2.7	5.0	2.0	78	96	78	63	49	45	Convulsions after 3 h 50 min
7/IV	3.0	5.0	2.0	91	97	90	78	56	52	Convulsions after 2-1/2 h
6/VI	2.4	5.0	2.0	100	88	75	60	55	50	Convulsions after 3 h
10/VI	3.1	5.0	2.0	83	90	78	70	50	45	Convulsions after 3 h 25 min

experiments the effect of serotonin was studied on the blood sugar level after preliminary administration of insulin to the animals. In the third series of experiments insulin was given after a preliminary injection of serotonin into the animals. Serotonin was injected both subcutaneously and intravenously, in doses of 2 and 5 mg/kg body weight. The glucose concentration was examined by the Fingol method [9].

TABLE 4. Effect of Serotonin, Injected after Preliminary Insulinization of Animals, on Blood Sugar Level of Animals

Date of investigation (1962)	Weight of animals (in kg)	Dose of insulin (in units/kg)	Dose of serotonin (in mg/kg)	Sugar level (in mg%)						Manifestations accompanying insulin hypoglycemia
				before injection of insulin	30 min after injection of insulin	time after injection of serotonin				
						30 min	1 h	2 h	3 h	
Subcutaneous injection of insulin and serotonin										
12/IV	2.9	2.0	2.0	103	55	52	41	50	45	Convulsions after 1 h 45 min
13/IV	2.5	2.0	2.0	107	63	47	45	40	50	Convulsions after 1 h 30 min
13/IV	2.6	2.0	2.0	96	66	60	65	65	72	No convulsions
13/IV	3.0	2.0	2.0	108	75	70	70	67	70	No convulsions
12/V	3.1	2.0	2.0	98	83	79	80	63	54	No convulsions
12/IV	2.9	2.0	5.0	105	65	55	50	59	54	Convulsions after 2 h
12/IV	2.5	2.0	5.0	103	75	63	55	52	41	Convulsions after 1 h 45 min
13/IV	2.6	2.0	5.0	96	66	60	65	65	72	No convulsions
14/IV	2.3	2.0	5.0	104	89	75	70	73	64	No convulsions
15/V	2.1	2.0	5.0	87	70	68	63	54	43	Convulsions after 3 h
Intravenous injection of serotonin and subcutaneous injection of insulin										
27/III	2.5	2.0	2.0	97	63	71	69	65	63	No convulsions
28/III	2.0	2.0	2.0	96	70	48	52	41	50	Convulsions after 3 h
29/III	2.5	2.0	2.0	100	66	64	61	55	55	No convulsions
29/III	3.1	2.0	2.0	106	80	85	73	70	60	No convulsions
30/III	2.5	2.0	2.0	112	70	59	57	66	60	No convulsions
27/III	2.7	2.0	5.0	111	76	63	67	60	39	No convulsions
28/III	3.5	2.0	5.0	103	77	70	52	52	39	No convulsions
29/III	2.6	2.0	5.0	100	79	61	66	45	50	Convulsions after 3 h
30/III	2.7	2.0	5.0	110	77	75	75	72	60	No convulsions
30/III	3.0	2.0	5.0	113	89	80	75	52	60	No convulsions

It will be clear from Tables 1 and 2 that the intravenous and subcutaneous injection of serotonin in a dose of 2 mg/kg had no effect on the blood glucose level of the rabbits and dogs. The changes observed, namely a slight increase in the sugar concentration over the initial level (after 30 min and 1, 2, 3, and 4 h) were not statistically significant ($P > 0.1$). After injection of serotonin intravenously into rabbits and subcutaneously into dogs in a dose of 5 mg/kg, the blood sugar level rose in these animals (results statistically significant, $P < 0.01$) and regained its normal level 120 min after injection of the drug. It must be pointed out that after injection of serotonin in a dose of 2 and 5 mg/kg into these animals they became lethargic and inactive, while the clotting power of their blood rose sharply.

Injection of insulin after the preliminary administration of serotonin caused, as usual, a lowering of the blood sugar level, and the extent of the fall in the sugar concentration was dependent on the dose of hormone injected. The insulin hypoglycemia was accompanied by nervous disturbances amounting, in some cases, to convulsions (Table 3). Neither the intravenous nor subcutaneous injection of serotonin into animals developing insulin hypoglycemia after injection of insulin affected the subsequent manifestation of the insulin effect (Table 4).

Hence, serotonin had no effect on the onset and development of the hypoglycemic syndrome in hyperinsulinism. Furthermore, in these experiments no epileptiform convulsions were observed in the animals receiving large dose of serotonin. Since this phenomenon arises after the injection of even very small doses of serotonin intracranially, the results of these investigations demonstrate that serotonin most probably does not pass through the blood-brain barrier, as many workers claim [7], or that it is destroyed on the way to the brain by the enzyme amine oxidase.

SUMMARY

In experiments on rabbits and dogs a study was made of the effect produced by various doses of serotonin on the blood sugar level and the insulin action. The first series of experiments dealt with determination of the blood

glucose level prior to and at various intervals after serotonin administration. In the second experimental series a study was made of serotonin effect on glycemic shifts against the background of preliminary animal insulinization. In the third experimental series insulin was administered after preliminary injection of serotonin.

The data obtained permit to draw the following conclusions:

1. Given both subcutaneously and intravenously in a dose of 2 mg/kg serotonin produced no effect on the blood glucose level. A rise of the blood sugar level followed the administration of 5 mg/kg in 60 min (the results are statistically authentic, $p < 0.01$); the sugar level becoming normal 120 min after serotonin injection.
2. Administration of serotonin in various doses against the background of developing insulin hypoglycemia failed to influence further manifestations of the insulin effect.
3. Serotonin produced no effect on the development of the nervous syndrome in hyperinsulinism.

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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.
