The Effect of Sensory Stimulation on the Blood Sugar Content of Rabbits, Splanchnicotomized or Suprarenalectomized.

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Nowadays it is a well established fact that the hyperglycaemia of the central origin is still causal, though in a less degree, in animals deprived of the suprarenal glands.¹⁾ Sensory stimulation is one of such agents (Starkenstein, Griffith and Kisch).

While the experiments carried out in the hands of Ciminata²⁾ should not be taken as supplying results quite contradictory to the view above mentioned, Schtscherbakow and his co-workers³⁾ not only failed to see an increase of the blood sugar concentration in cats on stimulating the central cut end of the sciatic nerve after either clamping the suprarenal veins or removing the glands themselves, but came to observe its fall. Lumley and Nice⁴⁾ removed the suprarenals from rats, and 7 to 9 days later stimulation with faradic current was tried. No increase was observed in their blood sugar on the average. The experimental conditions under which they worked seemed somewhat simpler than these of the Russian observers.

The experimental conditions preferred by them were rather those generally thought as improper for such kinds of experiments, but it seemed to me worth while to attack this problem again on this opportunity in order to make clear the scale of the share of the suprarenal glands in increasing the blood sugar content through sensory stimulation.

1) Satake, Tohoku Jour. of Exp. Med., 1926, 8, 26: Nearly complete reviews concerning this matter there. A report of Babkin, Journ. of Physiol., 1925-6, 59, Proc. lxvi (Cats & dogs, decerebrated, stimulation of central end of the sciatic nerve, removal of the suprarenals and section of the splanchnics diminish the reflex hyperglycaemia but not abolish it.) may be added further to complete the references.

2) Ciminata, Bull. e Atti d. R. Acc. Med. di Roma, 19(25-)26, 52, year, 231. Our thanks are due to Rev. P. Egli for translating this essay from Italian.

3) Schtscherbakow, Simnitzky, Wischnewsky and Dimitrijew, Pflügers Arch., 1930, 224, 670.

4) Lumley and Nice, Am. Jour. of Physiol., 1930, 93, 152.

Methods: Commonly male rabbits of good nutrition were experimented on, sometimes non-pregnant females also. Of the feeding nothing is to be added here to the modus given in several papers from this Laboratory, on the day before the sensory experiment the animal was brought into my laboratory room just after noon and no food was given.

Suprarenalectomy was carried out as usual in this Laboratory through the lumbar way, about three weeks being allowed to elapse from the right side removal to the left decapsulation, and no sensory experiment was run before the body weight recovered and the appetite and behavior looked wholly healthy. In fact the sensory stimulation was carried out 35 to 67 days after the last decapsulation.

Splanchnicotomy was also done through the lumbar route as described in a paper of Tada,⁵⁾ and actually done at once on both sides, and 21 to 68 days later the blood sugar observations were first carried out.

Sensory stimulation was done on the sciatic nerve. The animal was fastened on the table in a prone position and one side, the left side as a rule, sciatic nerve was laid bare and prepared the cephalad cut end for stimulation, and then the animal was freed. Ample time was allowed for the subsidence of the stimulation incident to this major operation. Stimulation was done by means of the induction shock current; the coil distance was taken as a rule as 7 cms., while that of 13 cms. can be first felt by the tongue. On stimulating the cephalad cut end of the nerve the animal was gently but firmly held down on the table by an assistant, the incision wounds were again opened and the nerve was irritated with a moderately strong tetanizing current for just one minute.

Sugar determination was done for blood samples taken from the ear vein of both sides which had been previously denervated, Hagedorn and Jensen's procedure being used.

RESULTS.

Sensory stimulation was tried on 13 normal rabbits, 8 male and 5 female, in 7 doubly splanchnicotomized, 6 male and one female, and in 5 doubly suprarenalectomized, male ones. One example is reproduced from each series in order to show the whole course of the blood sugar fluctuation, and all the data are summarized in three tables. To show the difference of the features in the three groups of animals at one glance further the average values were calculated according to

5) Tada, Tohoku Journ. of Exp. Med., 1932, 19, 409.

Intact animal.

7. III. 1931. Rabbit 7 ♂ 1.89 kilos.
 8:30-8:35 Great auricular nerves were cut.
 8:40-8:55 L sciatic nerve prepared.

Time	Blood sugar (%)	Frequency of respi- ration (per min.)	Body temperature (°C.)	Room temperature (°C.)	Remarks
1:15 p.m.	0.097	82	38.9	18.5	Pupils dilated at once.
		1:30-1:31 sciatic nerve stimulated.			
1:35	0.176	156	39.1	18.5	
1:38	0.185				
1:45	0.190	148	39.2	18.5	
1:52	0.149				
1:55	0.145				
2:00	0.158	146	38.9	19	
2:05	0.151				
2:10	0.156				
2:30	0.145	128	39.0	19	
2:40	0.136				
3:00	0.122	122	38.9	18.5	
3:20	0.132				
3:40	0.106	114	38.7	18.5	
4:00	0.108				
4:20	0.097	108	38.7	18	
4:40	0.092	106	38.6	18	

the series of experiments from all the data from all the animals and are given with the chart.

It is scarcely necessary to say that rabbits, regardless of whether they were operated on or non-operated, reacted to stimulation with squealing, struggling, etc., and that the initial value of blood sugar content in three kinds of rabbits was wholly the same.

In the normal rabbits the blood sugar concentration was invariably increased by sensory stimulation, the peak as 0.13% to 0.19%, and mean (of 13 cases) 0.15% being measured 5 to 46 minutes, mean about twenty five minutes after the stimulation. The ratio of the maximum value to the initial was 143-206, mean 167 against 100. 2 to 5 minutes after discontinuance of stimulation the blood sample was first drawn out, this sample was invariably proved to contain a somewhat large amount of sugar, especially in Experiments 2, 3, 5, 7, 9, and 10. In Rabbit 7 the sample collected 4 minutes after stopping the stimulation contained 0.176% sugar in contrast to 0.097% before the stimulation. Then the blood sugar increased commonly further, sometimes with some fluctuation, sometimes in a straight line, to the peak. In Rabbit 11 the elevation to the peak was made smoothly notwithstanding a small velocity of elevating and the lowness of the peak; in Rabbit 3 there was a depression in the ascending limb in spite of the

short time needed for reaching the peak (0.166% 14 minutes after the stimulation).

The descending limb of the hyperglycaemia was always very slow so that two to three hours or more were wanted to recover the initial level; in this limb there were invariably some fluctuations, it was never smooth. Some small concentration as 0.07% appeared only in a single case, Rabbit 3, two hours and three hours after the stimulation; it was interrupted with a small elevation as 0.09%. A small fall against the initial, as from 0.098% to 0.086% (Rabbit 1), was noted in a few cases 2-3 hours after the stimulation.

The body temperature ascended by 0.1 to 0.4°C in a few minutes to a half hour after the stimulation; in some cases the initial value or a little higher temperature was measured at the end of experiment, that is 3-4 hours after the stimulation, but in others the experiment was stopped with a small lowering of temperature, as reduction of 0.1-0.3°C.

The respiration became frequent on sensory stimulation and the pupils dilated at once ad maximum for a while.

Doubly splanchnicotomized rabbits, 7 in number, were utilized for the experiment, and yielded the results given in Tabele II, which apparently differ wholly from those in the normal rabbits.

Doubly splanchnicotomized rabbit.

6. V. 1931. Rabbit 18 ♂ 1.89 kilos.
(28. III. '31. 1.87 kilos. Splanchnic nerves doubly cut.)
5. V. Auricular nerves bilaterally cut.
8:00 a.m. L sciatic nerve prepared for stimulation.

Time	Blood sugar (%)	Frequency of respi- ration (per min.)	Body temperature (°C.)	Room temperature (°C.)	Remarks
2:20 p.m.	0.093	120	39.4	17	Pupil dilated.
	2:34-2:35 sciatic nerve stimulated.				
2:40	0.123	132	39.8	17	
2:45	0.121				
2:50	0.119	168			
2:55	0.117				
3:00	0.129	136	39.6	17.5	
3:10	0.107				
3:20	0.105				
3:35	0.098	130	39.5	18	
3:50	0.100				
4:05	0.086	128	39.3	18	
4:20	0.089				
4:35	0.093				
5:05	0.098	132	39.4	18.5	
5:35	0.095				
6:05	0.097	124	39.5	18.5	
6:35	0.098	118	39.3	18	

While the reactions of animals against the sensory stimulation, betrayed in the general behavior, pupile width, respiration and the body temperature, were wholly the same in both sets or further in the three, viz. all sets of experiments, the reaction visible in the blood sugar concentration was this time, that is in the bilaterally splanchnicotomized rabbits, very weak, through never wholly absent.

The maximum concentration detected after conducting tetanizing stimulation on the central cut end of the sciatic nerve was noted as 0.098% to 0.129%, mean 0.112%. In four out of seven rabbits the first blood sample taken 2 to 5 minutes after discontinuance of stimulation showed the greatest concentration, but in Rabbits 17, 18 & 15 the maximum was found respectively 30 minutes and 26 minutes after the discontinuance, and in Rabbit 14 the blood sugar contained in the second sample collected 7 minutes after the discontinuance of stimulation was very slightly greater than that in the sample taken 3 minutes previously. In Rabbits 14, 15, & 18 the first sample taken 3-5 minutes after stopping the stimulation had already a little greater amount of sugar compared with the initial, only in Rabbit 17 the samples obtained respectively 5 and 10 minutes after the stimulation were found to contain a little smaller amount of sugar than the sample before the stimulation.

After the maximum the blood sugar decreased step by step, with some fluctuations, and it is rather difficult to decide with definiteness when the initial value was regained, because of the very slow declination of the descending limb. In one example (Rabbit 20) it is clear that the hyperglycaemia lasted for only about 1.5 hours, and the sugar level continued to descend further, so that 0.08% sugar was estimated 3.5 hours after stimulation against 0.098% of the initial. It may be further said that the hyperglycaemia lasted in Rabbits 14, 15, 16, 17 & 19 for about 2 to 3 hours. No tendency to hypoglycaemia was detected in any case except Rabbit 20 above related. A fact that there are some certain fluctuations in the blood sugar concentration, besides the general inclination to increase and then to decrease, seems worthy of note.

In these rabbits the body temperature ascended a little, 0.2-0.4° being measured as the excess. The maximum height was reached in some cases in a few minutes and in others 0.25-0.5 hour after the stimulation, and then descended very slowly so that towards the end of the experiment, that is, 2 to 4 hours after the stimulation, the body temperature was a little below, 0.1-0.3°, than that before the stimulation.

Lastly the data from the bilaterally suprarenalectomized rabbits will be discussed. On receiving the faradaic stimulation for 60 seconds on the cephalad cut end of the sciatic nerve, the blood sugar content

increased in this kind of rabbits also, and really materially not inferior in degree to the normal ones, contrary to the rabbits doubly splanchnicotomized.

Doubly suprarenalectomized rabbit.

13. VI. 1931. Rabbit 25 ♂ 1.78 kilos.
 (25. II. '31. 1.65 kilos. R suprarenal gland removed.)
 (6. IV. 1.75 kilos. L gland removed.)
 10. VI. Auricular nerves bilaterally cut.
 9:00-9:10. L sciatic nerve prepared.

Time	Blood sugar (%)	Frequency of respi- ration (per min.)	Body temperature (°C.)	Room temperature (°C.)	Remarks
9:20 a.m.	0.098	102	38.9	17	Pupil dilated.
	9:29-9:30 sciatic nerve stimulated.				
9:35	0.167	138	39.2	17	
9:40	0.165				
9:45	0.156	152	39.2	17	
9:50	0.169				
10:00	0.178	146	38.9	18	
10:15	0.169				
10:30	0.151	138	38.7	18	
10:50	0.127				
11:10	0.119	124	38.8	18	
11:30	0.103	118	38.8	18.5	
12:00	0.100	120	38.6	18.5	
12:30 p.m.	0.096	116	38.6	19	
1:00	0.095	112	38.3	19	
1:30	0.096	118	38.4	19.5	

The greatest blood sugar concentration after the stimulation was 0.128% to 0.20%, mean 0.155%, which was measured 10 to 45 minutes after stopping the stimulation. The sample collected 5 minutes after the discontinuance betrayed already some degree of hyperglycaemia, as 0.163% in Rabbit 22 and 0.167% in Rabbit 25. In three rabbits (Nos. 21, 23, & 25) the blood sugar level reached the peak with fluctuations and really the peak was found 30 to 45 minutes after the discontinuance of stimulation. In the other two cases the blood sugar content 10 or 15 minutes after the stimulation was the greatest. After the peak was reached the sugar content showed a tendency to return to the initial, but slowly and with some fluctuations. At the end of observations extending for four hours no hypoglycaemia was observed, only in Rabbits 22 and 25 a slightly smaller concentration than the initial was estimated, but it was within the normal limits, as 0.087% and 0.095% respectively; and in these animals the value before the stimulation was again found respectively 2 and 3 hours after the stimulation. In the rest it was not again found.

The anal temperature ascended a little as usual, the excess was 0.2 to 0.4°C, and this was found 5–30 minutes after the stimulation. The time when the peak of the body temperature was noted did not coincide with that of the hyperglycaemia.

The transitory dilation of the pupils on the stimulation and accelerated breathing were found also as usual.

Solid circles with solid lines indicate: Mean blood sugar in 13 normal rabbits. Triangles with dash and dotted lines: That in 7 splanchnicotomized rabbits. Light circles with dotted lines: That of 5 suprarenalectomized ones.

That relation is shown in the chart; the blood sugar value before the stimulation is there taken as 100, and the average values of 13 normal rabbits are expressed with solid circles connected with solid lines, those of 7 doubly splanchnicotomized ones with triangles connected with dash and dotted lines and those of 5 doubly suprarenalectomized with light circles connected with dotted lines. The peak or plateau of the hyperglycaemia was a little higher in the doubly suprarenalectomized rabbits compared with the normal ones, and the descending limb well coincided for both kinds of rabbits. That the peak of the hyperglycaemia was rather higher on an average in the decapsulated than in the normal is due to that in Rabbit No. 22; if it be taken out of account the reverse holds true. The number of the present experiments, especially of the decapsulated was small; highly probably it may be justifiable to assume practically no material difference in the magnitude of the hyperglycaemia due to sensory stimulation between the normal rabbits and the decapsulated.

By this finding however we do not intend to deny any rôle of the augmented epinephrine secretion taking place on sensory stimulation in causing the hyperglycaemia simultaneously elicited. It is a well established fact that sensory stimulation evokes an augmented secretion of epinephrine, especially invariably when no anaesthesia is resorted to.⁶⁾ What share is played by the augmented secretion in eliciting the hyperglycaemia is still open to question, some quantitative information is needed.

By way of precaution it may be added that it was indispensable for stating the augmenting effect of sensory stimulation on the epinephrine output rate in the experiment of Russian writers³⁾ that the blood sample from the suprarenal vein be collected before the sensory stimulation as the control, and the rate of blood flow from that vein be noted. Further it may be added that it was puzzling in their paper compare, for example, Figure 1 and its description in the text.

SUMMARY.

Being led by two recent papers noting non-glycaemic action of the sensory stimulation in the cats when the suprarenal glands were excluded anatomically or from functioning, we have attacked this kind of experimentation again, that is sensory stimulation was tried on rabbits, normal, and long surviving either double splanchnicotomy or doubly suprarenalectomy. The cephalad cut end of the sciatic nerve was used for the sensory stimulation. The results are as follows: While the double splanchnicotomy diminishes on a large scale the magnitude of the hyperglycaemia due to sensory stimulation, the removal of the suprarenal glands does so only to a quite small extent or almost nothing.

6) Kodama, *Tohoku Journ. of Exp. Med.*, 1923, 4, 166, 1924, 4, 465; Sugawara, Watanabe and Saito, *Ibid.*, 1926, 7, 1; Satake, Sugawara and Watanabe, *Ibid.*, 1927, 9, 1. Rather complete literature there.

TABLE I.
Influence of sciatic nerve stimulation upon the blood sugar content of normal rabbits.
(Sciatic nerve stimulation 1 minute.)

No.	Sex	Date of experiment	Body weight (kilos)	Blood sugar				Frequency of respiration		Body temperature		Room temperature (°C.)
				Before stimulation (%)	Maximum during experiment (%)	Time to maximum (min.)	Time to recovery (hours)	Initial (per min.)	After stimulation (per min.)	Initial (°C.)	After stimulation (°C.)	
1	♂	3. II. 1931	2.11	0.086	0.142	46	2	82	118-148	38.8	38.9-39.1	18-19.5
2	♂	5. II. 1931	1.50	0.082	0.151	5	2½	106	110-152	39.0	39.1-39.3	17.5-19
3	♂	24. II. 1931	2.00	0.096	0.166	14	1	78	110-162	38.9	38.7-39.1	18-19.5
4	♀	26. II. 1931	2.55	0.091	0.132	34	> 3½	120	132-172	38.7	38.5-38.9	17.5-19.5
5	♂	3. III. 1931	1.98	0.075	0.153	24	> 4	68	98-152	38.6	38.5-38.8	18-19
6	♀	5. III. 1931	1.82	0.086	0.146	39	< 3	96	114-152	39.1	38.9-39.3	15-18.5
7	♀	7. III. 1931	1.89	0.097	0.190	14	3	82	106-156	38.9	38.6-39.2	18-19
8	♀	10. III. 1931	1.86	0.100	0.153	6	4	102	118-156	38.7	38.5-39.0	18-19.5
9	♂	12. III. 1931	2.11	0.098	0.179	14	2	76	116-156	39.0	38.7-39.2	18-19.5
10	♂	14. III. 1931	1.95	0.105	0.170	10	2½	92	114-152	39.1	39.0-39.3	17-19.5
11	♀	20. III. 1931	1.79	0.098	0.140	45	> 3½	116	118-146	38.8	38.7-39.1	17.5-19.5
12	♂	26. III. 1931	1.97	0.102	0.147	25	2	66	106-146	39.0	38.9-39.3	18-19.5
13	♀	16. V. 1931	2.02	0.087	0.136	20	2	102	118-186	39.1	39.2-39.6	17.5-20
			Mean	0.075-0.105	0.132-0.190	5-46						
				0.092	0.154	ca. 25						

TABLE II.
Influence of sciatic nerve stimulation on the sugar content of bilaterally splenectomized rabbits.
(Sciatic nerve stimulation 1 minute.)

No.	Sex	Splanchnicotomy		Date of experiment	Body weight (kilos)	Blood sugar						Frequency of respiration		Body temperature		Room temperature (°C.)
		Date of operation	Body weight (kilos)			Initial (%)	Maximum during experiment (%)	Time to maximum (min.)	Time to recovery (hours)	Initial (per min.)	After stimulation (per min.)	Initial (°C.)	After stimulation (°C.)			
14	♂	24. I. 1931	1.75	17. III. '31	1.75	0.091	0.110	7	>4.5	86	118-138	38.6	38.5-38.8	19-19		
15	♂	31. I. 1931	1.78	19. III. '31	1.84	0.089	0.098	26	3.5	96	118-152	39.1	38.9-39.3	18.5-19.5		
16	♂	5. II. 1931	1.95	24. III. '31	2.05	0.093	0.106	2	2	110	120-156	38.8	38.8-39.1	18.5-19.5		
17	♂	25. III. 1931	1.63	16. IV. '31	1.78	0.095	0.106	30	2	90	96-156	39.3	39.0-39.6	18-19.5		
18	♂	28. III. 1931	1.87	6. V. '31	1.89	0.093	0.129	30	1½	120	118-168	39.4	39.3-39.6	17-18.5		
19	♂	27. III. 1931	1.91	20. V. '31	2.05	0.093	0.111	5	2	56	118-152	38.6	38.3-38.8	17-18.5		
20	♂	27. III. 1931	1.98	15. VI. '31	1.98	0.098	0.124	5	1½	68	90-136	38.2	38.0-38.5	18-19.5		
					Mean	0.089-0.098	0.098-0.129	2-30								
						0.093	0.112	15								

TABLE III.

Influence of sciatic nerve stimulation upon the blood sugar content of bilaterally suprarenalctomized rabbits.
(Sciatic nerve stimulation 1 minute.)

No.	Sex	Suprarenalectomy				Date of experiment	Body weight (kilos)	Blood sugar						Frequency of respiration		Body temperature		Room temperature (°C.)
		r.		l.				Initial (%)	Maximum during experiment (%)	Time to maximum (min.)	Time to recovery (hours)	Initial (per min.)	After stimulation (per min.)	Initial (°C.)	After stimulation (°C.)			
		Date of operation	Body weight (kilos)	Date of operation	Body weight (kilos)													
21	♀	26. II. '31	1.75	6. IV. '31	1.79	11. V. 1931	1.90	0.091	0.128	45	> 4	104	116-138	38.5	38.3-38.7	17-19		
22	♀	6. II. '31	1.715	10. III. '31	1.85	13. V. 1931	2.07	0.105	0.201	15	2	86	96-162	38.7	38.7-39.1	15-18.5		
23	♀	13. II. '31	1.385	2. IV. '31	1.715	25. V. 1931	1.72	0.091	0.149	30	3½	98	118-152	38.5	38.4-38.9	17-19		
24	♀	13. II. '31	1.465	2. IV. '31	1.74	27. V. 1931	1.97	0.086	0.129	10	< 3½	66	96-136	39.2	39.0-39.5	17-19		
25	♀	25. II. '31	1.65	6. IV. '31	1.75	13. VI. 1931	1.78	0.098	0.169	30	3	102	112-152	38.9	38.3-39.2	17-19.5		
							Mean	0.086-0.105	0.128-0.201	10-45								
								0.094	0.155	ca. 25								