The Hyperglycaemia after Potassium Cyanide in Rabbits, Splanchnicotomized or Suprarenalectomized.

By

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Nearly all the observers have agreed in eliciting hyperglycaemia by giving hydrocyanic acid or its salts to rabbits or dogs.^{1,2,4,5,6)} These were administered intravenously²⁾ or subcutaneously. Only Yano and Kirita³⁾ were not only unable to detect an increase in the blood sugar concentration in rabbits by letting them inhale hydrocyanic gas, but also on the contrary they detected a remarkable decrease as to one third of the initial; the hypoglycaemia did not appear when the gas was given to rabbits, doubly splanchnicotomized. The rabbits, operated on similarly, were also used by Kudo⁶⁾; according to him hydrocyanic acid induces the first transitory hyperglycaemia and the second one, and the splanchnicotomy diminishes the first increase and wholly abolishes the second. Kawamura⁴⁾ is apt also to assume that the hyperglycaemia is divided in two by interpolating the hypoglycaemic spell.

In order to know whether or not cyanide hyperglycaemia is of the central origin and whether or not the suprarenal glands are dispensable in causing the hyperglycaemia by giving cyanide, the present investigations were performed on rabbits, normal, splanchnicotomized and suprarenalectomized as well.

1) Zillessen, Hoppe-Seylers Zeitschr., 1891, **15**, 387 (Cyan acid solution per os or subcutaneously, slight hyperglycaemia, no glycosuria in rabbits, but slight glycosuria in dogs).

2) Tatum and Atkinson, Jour. of Biol. Chem., 1922, **54**, 331.

3) Yano and Kirita, Chugai Iji Shimpō, 1926, 810.

4) Kawamura, Kyoto-Ikadaigaku-Zasshi, 1928, **2**, Part B, 155 (German).

5) Oda, Nihon Naibumpitsu Gakkai Zasshi, 1929, **5**, 393.

6) Kudo, Manshu Igakkai Zasshi, 1930, **13**, 413.

Mostly male rabbits were used, but in a few cases female, but non-pregnant ones were experimented on. All the techniques in feeding and treating the animals, cutting the splanchnic nerves and removing the suprarenals and determining the blood sugar content, etc., are given in my previous paper.⁷⁾

1% KCN (Merck) solution, prepared freshly every time, was injected under the skin of rabbits, always in a dose of 2.5 mgrms. KCN per kilo of body weight.

At the end of the paper are three tables compiled from the data in three kinds of animals, normal, suprarenalectomized and splanchnicotomized.

Normal Rabbits: The data from 7 male, normal rabbits may be mentioned firstly.

EXAMPLE I.

Normal rabbit, 2. ♂.

(N. auricularis magnus and the cervical sympathetic nerve were cut on the left side)

10. IV. 1931. ♂ 1.95 kilos.

Time	Blood sugar (%)	Frequency of respiration (per min.)	Body temperature (°C.)	Room temperature (°C.)	Remarks
11:00 a.m.	0.098	90	38.7	16.5	
11:15	Injected 2.5 mgrms. potassium cyanide per kilo body weight subcutaneously.				
11:27	0.156	150	38.6	16.5	3 minutes after injection the respiration accelerated gradually, further two minutes later severe convulsions set in, then the animal fell on its side, convulsions occurred from time to time. Cornea reflex disappeared, respiration very deep. Thirty minutes after injection the animal got up scarcely, respiration 108 a minute, 5 minutes later the general behavior showed a tendency of recovery, respiration 120; 10 minutes further later the recovery became somewhat evident, respiration 180. 60 minutes after injection the animal quiet, apparently normal.
11:34	0.187	104		17	
11:40	0.206	72	38.5		
11:45	0.225	100			
11:50	0.229	120	38.3	17.5	
12:00 m.	0.216	180			
12:15 p.m.	0.208	108		17.5	
12:45	0.203	66	38.5		
1:15	0.181	66		18	
1:45	0.163	66	38.6		
2:15	0.134	66		18	
2:45	0.105	72	38.6		
3:15	0.102	60			
3:45	0.095	66	38.7	18.5	
4:15	0.096	72	38.8		

7) Ohmi, Tohoku Jour. of Exp. Med., 1933, 20, 498.

On receiving the hypodermical injection the breathing became generally largely accelerated for a while, and then deep. 3 to 5 minutes after the injection all the rabbits, except No. 3, became uneasy, the equilibrium of the body seriously disturbed, lay down and convulsions of various degrees set in. When the seizures were very violent, the respiration stopped though quite transiently. The heart beat very weakly. When convulsions no more occurred, the body then became flaccid, the reflexes disappeared, the paralytic stage thus began. The Cheyne-Stokes' type of respiration was very often observed just before and during the paralytic stage. When the attack of convulsions was manifested repeatedly, as in Nos. 1, 2, 4 & 5, the paralytic stage also lasted long; Rabbit No. 5 was still paralytic at the end of 5 hours of poisoning.

The anal temperature descended a little on receiving cyanide. A decrease of 0.2 to 0.6° was the maximum, which was estimated a half hour after the injection to 3 hours thereafter. Afterwards the body temperature showed a tendency to recover or further to exceed finally the initial though very slightly.

The blood sugar content of 7 normal rabbits without exception increased on injecting cyanide. The maximum as 0.137% to 0.229%, mean of 7 cases 0.185% was reached about 30 minutes to 100 minutes after the injection, and then the sugar level descended gradually. In the observation extending for 4 to 5 hours after the injection no hypoglycaemic stage was found, although in some cases as Nos. 1, 2, 5, 6 a little smaller content compared with the initial was found, as from 0.098% to 0.09% in No. 1. Notwithstanding the sugar estimations were done every 5 minutes during 30 minutes after the injection, every 10 minutes during next thirty minutes and then every thirty minutes during the rest of the experiment, I have not been able to see a case of hyperglycaemia with two summits in the whole course of cyanide poisoning, as some experimentalists have written.

In two cases out of 7, the blood sugar content 5 minutes after the injection was definitely smaller than the initial, but the inferiority was too small to speak of the appearance of hypoglycaemia; and the next collected 5 minutes later or the third sample collected 10 minutes later was identical with the initial. It might be difficult or unjustifiable to take this quite small and transitory diminution in the blood sugar as a small copy of the hypoglycaemia detected by Yano and Kirita. The latter was of remarkable degree, as about 0.035% in two cases and 0.052% and 0.050% in the other two. They failed further to find any occurrence of hyperglycaemia. Their findings are more remarkable in that they were able to see a definite hyperglycaemia in rabbits by letting them breathe CO gas, the common outcome.

While Kawamura and Kudo obtained only a small degree of hyperglycaemia and sometimes rather inconstant outcome by giving similar doses as the present, the hyperglycaemia occurred in the present rabbits in a moderately great magnitude always, as Tatum and Atkinson.

The peak of hyperglycaemia did not coincide in the time relation with the maximum acceleration in the respiration frequency and the minimum of the anal temperature. The peak of hyperglycaemia was determined when the respiration was still accelerated, as in Nos. 1, 2, 3 & 6, but in the three others it was detected after the respiration rhythm had already become much less than the initial. The minimum anal temperature was noted sometimes earlier, sometimes much later than the peak of hyperglycaemia; in two cases, No. 2, given as Example, and No. 6, they coincided.

Doubly Suprarenalectomized Rabbits: All male; 35 to 72 days were allowed to elapse from the second decapsulation to the cyanide injection. The same dosage of potassium cyanide was resorted to. The initial blood sugar was 0.091 to 0.104% in 4 so operated rabbits, not a whit different from the values found in normal animals. Similar poisoning symptoms were elicited in these animals as in the normal ones, as shown in a protocol reproduced here. In Rabbits Nos. 8 & 10 the Cheyne-Stokes' type of respiration was also observed.

EXAMPLE II.

Doubly suprarenalectomized rabbit.

20. II. 1931. 1.57 kilos. R suprarenalectomy.

4. IV. 1.95 kilos. L suprarenalectomy.

6. IV. R n. auricularis magnus and the cervical sympathetic nerve cut.

Time	Blood sugar (%)	Frequency of respi- ration (per min.)	Body tem- perature (°C.)	Room tem- perature (°C.)	Remarks
2:00 p.m.	0.096	112	38.9	18.5	Violent convulsions occurred 5 minutes after injection and during next ten minutes the animal was attacked by severe ones, and the respiration deep. 20 minutes after injection breathing frequent, and the animal lay down. 45 minutes after injection the general behavior indicates a tendency to recover, and 15 minutes later it appeared wholly recovered.
2:10	Injected 2.5 mgrms. potassium cyanide per kilo body weight subcutaneously.				
2:15	0.098	168	38.7	18.5	
2:20	0.115	78	38.5		
2:25	0.166	66	38.4	18.5	
2:30	0.173	124	38.4		
2:35	0.175	146	38.6	19	
2:40	0.176	150	38.6		
2:50	0.167	138	38.6		
3:00	0.162	134	38.7	19	
3:10	0.140	130	38.8		
3:30	0.133	132	38.9	19	
4:00	0.096	118	38.9		
4:30	0.095	124	39.1	18	
5:00	0.093	128	39.1		
6:00	0.095	126	39.0	18	

The blood sugar concentration increased definitely on cyanide injection without one exceptional case. The peak was of such values as 0.142 to 0.176%, a little inferior to that in the normal rabbits, and it was reached on an average a little earlier too. But if two cases,

Nos. 5 & 7, of normal rabbits which betrayed somewhat large degree of hyperglycaemia as 0.245% and 0.208% respectively, be left out of consideration, the time needed for reaching the peak of hyperglycaemia well coincides in both sets of animals, normal and doubly suprarenalectomized. The time with which the descending limb of hyperglycaemia achieved the initial value of blood sugar, was only a little shorter on an average in this set of experiments than in the normal rabbits.

Only in a single case, namely in No. 10, the blood taken 5 minutes after the injection contained a little smaller amount of sugar compared with the initial. 0.091% and 0.086% were such figures. In the descending limb of hyperglycaemia no special depression was obtained, that is the hyperglycaemia disappeared gradually and smoothly. Only a small diminution in the blood sugar concentration from the initial appeared in the later period of experimentation extending for 4-5 hours, but the absolute amount was never smaller than 0.09%.

The time relation between the peak of hyperglycaemia, the maximum frequency of respiration and the minimum anal temperature was similar with the set of normal rabbits.

Doubly splachnicotomized Rabbits: The outcome of this set of rabbits largely differed from the other two. At least two weeks were allowed between the splachnicotomy and the cyanide experiment, as shown in Table III.

11 rabbits, involving two females, were experimented on. No alteration is necessary in the above description of the general intoxication symptoms in the normal rabbits.

The initial blood sugar level was 0.088% to 0.096%, mean 0.092%. On receiving cyanide in the same dose as the other groups of rabbits, the blood sugar content fluctuated very slightly contrary to the other groups; in 8 of 11 cases the sugar content increased to from 0.105% to 0.123%, very small, though unmistakable, commonly 15 minutes to 1 hour after the injection, seldom 2.5 hours and 3.5 hours thereafter. The latter, Nos. 15 and 19, may be taken as the second hyperglycaemic period of Kawamura and Kudo, for the time when it appeared checks with that given by them, and in the earlier stage the rabbits showed quite transitorily a small increase in the blood sugar. But we have found such cases only exceptionally, so that we hesitate to say that their findings are an exaggeration of those detected in these two rabbits. In the rest, that is Nos. 13, 17 and 22, no increase was witnessed at all in the blood sugar concentration.

The hyperglycaemia in 6 rabbits, though far small in intensity, can be taken as a small manifestation of the hyperglycaemia due to cyanide by judging from the time course of the level variation.

EXAMPLE III.

Doubly splanchnicotomized rabbit.

(25. III. 1931. 1.5 kilos. Double splanchnicotomy & denervation of R ear.)

21. IV. 1931. Rabbit ♂ 1.51 kilos.

Time	Blood sugar (%)	Frequency of respiration (per min.)	Body temperature (°C.)	Room temperature (°C.)	Remarks
2:50 p.m.	0.091	118	38.9	16.5	
3:00	Injected 2.5 mgrms. potassium cyanide per kilo body weight subcutaneously.				
3:05	0.098	146	38.7	16.5	5 minutes after injection the animal uneasy, respiration remarkably accelerated. 10 minutes later slight convulsions, apathetic, and lay down. 60 minutes after injection some sign of recovery. 3:20 apparently wholly normal.
3:10	0.097				
3:15	0.100	150	38.5	17	
3:20	0.107				
3:30	0.123	126	38.6	17.5	
3:40	0.123				
3:50	0.119	92	38.4	17.5	
4:00	0.117				
4:15	0.120	88	38.5	17	
4:30	0.118				
5:00	0.102	102	38.7	16.5	
5:30	0.093				
6:00	0.092	106	38.9	16	
6:30	0.090				
7:00	0.090	108	39.1	16	

This time a remarkable decrease was discovered in the blood sugar in a few cases. Rabbit 13 developed the hypoglycaemic spell soon after the poisoning, and so small a content as 0.052% was measured 20 minutes after the injection, and this spell lasted for 4.5 hours, but at the end of the experiment, that is 5 hours after the injection just the initial value was again noted. A hypoglycaemia as 0.074% occurred in Rabbit 17, and the hypoglycaemic period lasted also long in this case. Somewhat low concentration of the blood sugar was also measured in Rabbit 14(0.08%), Rabbit 21(0.084%) and Rabbit 22 (0.078%) only, in the remainder the content lower than the initial was never discovered through the whole routine of experiment covering 4-5 hours. The extensive hypoglycaemia visible in Rabbits 13 and 17 was noted in the paper of Yano and Kirita, but they saw such a phenomenon in normal rabbits, and when the splanchnic nerves were interfered with it disappeared totally, a rather diametrically opposite finding.

In order to show at a glance the effect of the double suprarenal-ectomy and of the double splanchnicotomy upon the carbohydrate metabolism disturbance due to the cyanide poisoning, the following chart is constructed. Solid circles connected with solid lines indicate

The initial values of blood sugar content are taken here as 100. Solid circles with solid lines indicate the average of 7 normal rabbits; light circles with dotted lines that of 4 doubly suprarenalectomized; triangles with dash and dotted lines that of 11 doubly splanchnicotomized.

the average blood sugar fluctuation of 7 normal rabbits, light circles with dotted lines the mean of 4 doubly suprarenalectomized, and lastly triangles with dash and dotted lines that of 11 double splanchnicotomized. The initial value has been taken as 100.

SUMMARY.

Potassium cyanide was hypodermically injected in the dose of 2.5 mgrms. per kilo of body weight into rabbits, normal, doubly suprarenalectomized and doubly splanchnicotomized as well.

A hyperglycaemia of a moderate strength occurred in normal rabbits constantly, whereas some experimentalists using a similar dosage have failed to elicit such a constant outcome.

Double suprarenalectomy did not largely interfere with the magnitude of hyperglycaemia due to cyanide, while double splanchnicotomy was capable of very conspicuously abolishing the effect of cyanide upon the blood sugar concentration.

It is thus elucidated that the hyperglycaemia in the cyanide intoxication is to a very large extent of the central origin, but existence of the suprarenal glands has only a small share in eliciting this hyperglycaemia.

TABLE I.

Effect of potassium cyanide upon blood sugar in normal rabbits.

(Potassium cyanide 2.5 mgrms. per kilo of body weight subcutaneously.)

No.	Sex	Date of experiment (1931)	Body weight (kilos)	Blood sugar (%)			Time to recovery (hours)	Frequency of respi- ration (per min.)		Body temperature (°C.)		Room temperature (°C.)
				Initial	Maximum during ex- periment	Time to maximum (min.)		Initial	After injection	Initial	After injection	
1	♂	9. IV.	2.13	0.098	0.174	50	2	110	120-240	38.2	38.1-39.1	17 -19
2	♂	10. IV.	1.95	0.098	0.229	35	4.5	90	60-180	38.7	38.3-38.8	16.5-18.5
3	♂	11. IV.	1.86	0.099	0.137	30	3.5	84	92-126	38.8	38.5-38.9	17 -18.5
4	♂	12. IV.	1.75	0.096	0.157	40	3	102	74-180	38.8	38.2-38.8	17 -18
5	♂	13. IV.	1.75	0.091	0.245	90	2.5	108	72-150	38.7	38.2-38.7	16.5-18
6	♂	28. IV.	1.92	0.098	0.151	30	3	118	68-160	39.0	38.7-39.1	17.5-19
7	♂	1. V.	2.07	0.097	0.208	105	>4	98	36-150	39.1	38.5-39.1	17 -18.5

TABLE II.

Effect of potassium cyanide upon blood sugar of bilaterally suprarenalctomized rabbits.

(Subcutaneous dose of potassium cyanide: 2.5 mgrms. per kilo of body weight.)

No.	Sex	R suprarenal-ectomy		L suprarenal-ectomy		Date of cyanide experiment (1931)	Body weight (kilos)	Blood sugar (%)				Frequency of respiration (per min.)		Body temperature (°C.)		Room temperature (°C.)
		Date of operation (1931)	Body weight (kilos)	Date of operation (1931)	Body weight (kilos)			Initial	Maximum during experiment	Time to maximum (min.)	Time to recovery (hours)	Initial	After injection	Initial	After injection	

TABLE III.
Effect of potassium cyanide upon blood sugar of bilaterally splachnicotomized rabbits.
 (Subcutaneous dose of potassium cyanide: 2.5 mgrms. per kilo of body weight.)

No.	Sex	Splachnicotomy		Date of cyanide experiment (1931)	Body weight (kilos)	Blood sugar (%)				Frequency of respiration (per min.)		Body temperature (°C.)		Room temperature (°C.)		
		Date of operation (1931)	Body weight (kilos)			Initial	Maximum during experiment	Time to maximum (min.)	Time to recovery (hours)	Initial	After Injection	Initial	After Injection			
8	♂	20. II.	1.57	4. IV.	1.95	16. VI.	1.88	0.096	0.176	30	2	112	66-108	38.9	38.4-39.1	18 -19
9	♂	20. II.	1.63	2. IV.	1.90	7. V.	1.85	0.099	0.148	30	>4	98	82-168	39.0	38.5-39.1	17 -18.5
10	♂	26. II.	1.75	6. IV.	1.79	11. V.	1.90	0.091	0.171	45	3	112	64-146	38.8	38.5-38.9	18 -19.5
11	♂	6. II.	1.72	10. III.	1.85	13. V.	2.07	0.104	0.142	30	2.5	102	42-252	39.1	38.3-38.9	18.5-19.5

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<i>Effect of potassium cyanide upon blood sugar of bilaterally splanchicotomized rabbits.</i>														
(Subcutaneous dose of potassium cyanide: 2.5 mgrms. per kilo of body weight.)														
No.	Sex	Splachnicotomy		Date of cyanide experiment (1931)	Body weight (kilos)	Blood sugar (%)				Frequency of respiration (per min.)		Body temperature (°C.)		Room temperature (°C.)
		Date of operation (1931)	Body weight (kilos)			Initial	Maximum during experiment	Time to maximum (min.)	Time to recovery (hours)	Initial	After Injection	Initial	After Injection	
12	♀	5. II.	1.78	13. IV.	1.95	0.091	0.107	45	>4	148	142-180	39.1	38.5-39.1	16 -17
13	♀	17. III.	1.68	14. IV.	1.75	0.096	0.095			102	126-160	38.9	38.4-39.0	16 -17
14	♀	31. I.	1.75	15. V.	1.89	0.091	0.116	50	1.5	98	116-150	39.0	38.5-38.9	16 -17
15	♀	25. III.	1.71	20. IV.	1.71	0.088	0.122	210		124	94-152	39.1	38.4-38.9	16 -17
16	♀	25. III.	1.50	21. IV.	1.51	0.091	0.123	30	3.5	118	92-146	38.9	38.4-39.1	16 -17.5
17	♀	27. III.	1.80	22. IV.	1.88	0.092	0.091			110	86-132	39.1	38.5-38.9	16.5-17.5
18	♀	28. III.	1.72	5. V.	1.72	0.096	0.114	15	>4.5	98	72-142	39.2	38.6-38.9	17.5-18.5
19	♀	28. III.	1.87	6. V.	1.89	0.095	0.109	150	3.5	130	60-148	38.8	38.3-38.9	16.5-18
20	♀	28. IV.	1.86	16. V.	2.02	0.088	0.123	40	3	112	60-148	39.0	38.3-38.7	17 -18.5
21	♂	27. III.	1.91	20. V.	2.17	0.095	0.105	40	1.5	132	66-240	38.7	38.3-38.9	17.5-18.5
22	♂	29. III.	1.77	23. V.	1.98	0.093	0.093			118	42-240	39.2	38.4-39.0	17 -18.5