XXXVII. THE EFFECT OF GUANIDINE DERIVATIVES ON TISSUE RESPIRATION.

BY CONSTANȚA BANU AND NICOLAI GAVRILESCU.

From the Institute of General Physiology, Bucarest.

(Received November 23rd, 1933.)

THE full review of the problem of tetania parathyreopriva recently published by Thomson and Collip [1932] makes it clear that many points in connection with the biochemical mechanism of the production of tetany remain open to question. Whilst it is universally agreed that the outstanding chemical change to be observed in tetania parathyreopriva is the lowering of the blood-calcium, it is still maintained by some authors that this phenomenon is incidental and is only one result of the general intoxication with guanidine derivatives which they regard as the primary cause of the condition.

There is at least no doubt that guanidine derivatives do produce symptoms of tetany, when administered in amounts so small as to indicate that the effect is a genuine intoxication and is not referable to any gross change such as a shift in the acid-base balance of the blood due to the basic character of the guanidine.

It is evident that any information as to the actual physiological effect of guanidine may be expected to be of use in elucidating the mechanism of the production of tetany by this substance and in helping to solve the further question as to whether intoxication with guanidine has in fact anything to do with tetania parathyreopriva.

The object of the present note is to describe the effect of guanidine derivatives on the respiration of isolated tissues.

EXPERIMENTAL.

The statement of Meyerhof [1921] that guanidine depresses the rate of yeast fermentation was confirmed.

For our own investigation we have used for the most part the brains of pigeons and rats; in addition experiments have been made with rat's liver and muscle and with rabbit's blood and nerve. The guanidine derivatives employed were guanidine hydrochloride and carbonate and methylguanidine hydrochloride.

The oxygen consumption of the tissues in air was measured in Dixon and Elliott's [1930] modification of the Barcroft apparatus, the details of the method being the same as those described in a former paper [Gavrilescu and Peters, 1931] except for the preparation of the material. It has been found that in experiments of this type the fineness and uniformity of division of the tissue are of the greatest importance if concordant results are to be obtained; discrepancies previously observed [*cf.* Gavrilescu and Peters, 1931] are probably to be ascribed to insufficient attention to this point. In the present series the liver, removed immediately after the death of the animal, was forced with a bone spatula through a fine sieve; the muscles were crushed in a Latapie grinder. In this way

the tissues were obtained in a finely divided and homogeneous condition, and duplicate determinations usually showed differences of less than 2 %.

0.1 g. of tissue was suspended in 3 ml. Ringer solution in the shaking-bottle of the Barcroft apparatus; in the case of experiments with guanidine derivatives the latter were added, immediately before placing the apparatus in the thermostat, in the form of 0.1 ml. of a 1.5 % solution; the final concentration of guanidine derivative was therefore 0.05 %. In a few experiments (see Table I) this concentration was increased. No change in p_H resulted from the additions of guanidine derivatives. The results are shown in Table I.

Table I.

Average oxygen uptake in mm.³/g./hr.

	Control	Guanidine	Para- thyrene	Guanidine and para- thyrene	% lowering by guanidine
A. Pigeon's brain	1428	1291			9.6
	1497	1399			6.5
	1516	1468			3.1
	1638	1444	1564		11.9
	1521	1258	1464		17.3
	1336	1239	1286		7.1
	1667	1576 (1592, 1341)*			5.4 (5.0, 19.6)
	1344	1329 (1252, 1053)*			1.2 (6.8, 21.7)
B. Rat's brain	1723	1515	1727	1558	12
	1375	1291	1403		6.1
	1744	1347	1629		22.7
	1610	1476	1621		8.3
	1560	1347	1741	1503	7.2
	1777	1567	1604		11.9
	1476	1287			12.9
	1734	1377†	1604	1420†	20.6
	1763	1427†	1747	1418†	19
	1728	1435†	1687		17
C. Rat's liver	572	536	544	540	6.3
	655	611			6.7
	706	692			—
	755	722			4.4
	974	1076			—
	572	573			—
	570	542			5.0
D. Rat's muscle	703	611			13
	175	222			—
	244	268			—
	253	215			15
	286	215			25
E. Rabbit's blood	149	156	191		—
	245	224	222	229	8.6
	222	207	234	182	7.1
	226	219			3.2
	200	191			4.5
	316	265			16
F. Rabbit's sciatic nerve	349	311			10
	277	207			25

* Guanidine concentrations 0.25, 0.5, 1.2 %.

† Methylguanidine.

In Table II are seen the results of an attempt to perform a similar experiment *in vivo*. Col. I shows the oxygen uptakes of the brains of six normal rats and col. 2 those of the brains of three rats killed at the height of the symptoms of tetany induced by intraperitoneal injection of 0.5 g./kg. of guanidine.

Table II.

Oxygen uptake of rat's brains in mm.³/g./hr.

Normal brains	Brains of animals killed at height of tetany after intraperitoneal injection of 0.5 g./kg. guanidine or methylguanidine
1723	1283
1744	1511
1610	1594
1734	—
1763	—
1728	—
Average 1717	1462

DISCUSSION.

It is clear from Tables I and II that in almost all cases the presence of guanidine derivatives has a significantly depressant action on the oxygen uptake of the tissues examined. It may be noted that the effect is less marked with pigeon's brain than with rat's brain, and this may be correlated with the known fact that the toxic dose of guanidine is about twice as high for pigeons as for rats.

It seems evident therefore that the general toxic effect of guanidine, leading to the production of symptoms of tetany, is to be ascribed in part at least to depression of tissue metabolism, in particular the metabolism of the brain. It is possible that this depression may lead to increased irritability of the respiratory centre and hence to alkalosis owing to excessive pulmonary ventilation.

The few experiments in which parathyrene was added gave no indication of a direct antagonistic action between the parathyroid hormone and the guanidine derivatives; our work does not therefore so far throw any light on the possible connection of guanidine intoxication with tetania parathyreopriva.

SUMMARY.

The oxygen uptake of isolated tissues (brain, liver, muscle) is significantly depressed by the presence of guanidine or methylguanidine in approximately 0.05 % concentration.

The oxygen uptake of the brain of rats poisoned with guanidine is lower than that of normal rat's brain.

We are indebted to Prof. I. Cantacuzino for help with the animal experiments.

REFERENCES.

- Dixon and Elliott (1930). *Biochem. J.* **24**, 820.
 Gavrilescu and Peters (1931). *Biochem. J.* **25**, 2150.
 Meyerhof (1921). *Pflüger's Arch.* **188**, 114.
 Thomson and Collip (1932). *Physiol. Rev.* **12**, 309.