A NOTE ON PURINE METABOLISM IN HIBERNATING ANIMALS

BY E. L. KENNAWAY, M.A., M.B., B.CH. OXON., *Demonstrator of Physiology, Guy's Hospital; late Hulme Research Student, Brasenose College, Oxford*

From the Physiological Laboratory, Guy's Hospital

(Received May 27th, 1910)

An increased output of purine compounds has been observed in man in various conditions which are associated with increased production of heat.

Cathcart and Leathes¹ showed that exposure to cold produced a rise in the amount of endogenous uric acid excreted. The subject of their experiments stripped and remained at rest for between two and three hours, the skin being kept wet by frequent immersion in cold water. The rectal temperature was by these means reduced about 0.5°. The output of uric acid rose above the normal level during the exposure to cold, and remained above it throughout the ensuing twenty-four hours, the amount excreted during this time being in one experiment 80 per cent. greater than the average.

Again, in conditions of fever, the excretion of large amounts of purine bases,² and of uric acid,^{3, 4} has been observed.

The increased output of purines in these cases might have been due (1) to liberation of purines from the nucleo-proteins of the tissues; (2) to

a synthesis of purines; (3) to diminished destruction of uric acid. Recent experiments on the destruction of uric acid by human tissues *in vitro* have, however, given negative results.⁵ Analyses of urine do not allow one to decide between these three possibilities. Dr. Pembrey suggested that the question might be investigated further in hibernating animals. During the awakening from hibernation a very rapid rise of body temperature (e.g., of 19° in forty-two minutes) takes place.⁶ The dependence of this rise of temperature upon increased production of heat is shown by the fact that the respiratory exchange is greatly increased, in some cases about a hundred fold, at the time of awakening; moreover, on the assumption that the substance oxidised at this time is fat, it has been calculated that the combustion indicated by the respiratory exchange would provide amply for the observed heating of the body.⁶ Such animals, therefore, provide material for ascertaining whether any change in the total purine content of the body is associated with an increase in the production of heat.

Dormice were used for these experiments. A large number were obtained in the autumn, and were fed on grain, carrots, chestnuts and apples. The estimations of purines were made by the method of Burian and Walker Hall.⁷ The intention was to make duplicate estimations (1) before, (2) during, hibernation; (3) during, (4) after, awakening; but the high death rate allowed only five estimations, involving a total of fifty dormice, to be made. However, the close agreement of the results seems to make them worth consideration. No attempt was made to obtain a further supply of dormice in the spring, as it was desirable that all should have been kept under the same conditions throughout. Owing to the exceptionally mild winter, the animals never remained torpid for more than a few days at a time. At the end of February, therefore, when there seemed to be no prospect of a period of natural hibernation, the cages were placed in a cooled chest (temp. 5°); the animals became torpid during the same day, and were allowed to remain in this state for four days. The body temperature, taken within the coil formed by the rolled-up body, was at this time from 6·3° to 8·2°; the reading obtained in this way is 1° to 2° lower than the rectal temperature.⁶ Those which were to be awakened were taken to a warm room; in about an hour they were quite active, the body temperature being then from 22° to 34°. They were killed within two hours of removal from the cooled chest.

	Number of mice	Weight of mice	Mean weight of mouse	Weight of tissue after mincing	PURINE NITROGEN		
					Total	Per cent. of tissue	Per mouse
<i>Before Hibernation</i>		g.	g.	g.	mg.		mg.
October 11th	12	171.5*	14.3	165.5	126.7	0.077	10.58
November 1st	12	171.5*	14.3	166.2	138.7	0.083	11.58
<i>Hibernating</i>							
March 5th	10	136.1	13.6	133.2	109.1	0.081	10.9
<i>Waking</i>							
March 1st—A	8	121.1	15.1	116.9	125.16	0.107	15.65
March 1st—B	8	118.7	14.8	114.2	118.30	0.104	14.79

The percentage of purine nitrogen found in the waking dormice is over 30 per cent. higher than that found before or during hibernation. This difference cannot be attributed to loss of fat during the winter, since those mice which were killed at the same time, but in the torpid state, show no increase in comparison with those killed in the autumn. Moreover, such a concentration of purines would not be produced even by the removal of all the fat in the body, since the greatest proportion of fat which has been found in autumn dormice of the weight of those under consideration is 17 per cent.⁸

Again, the difference observed cannot be due to the loss of body weight brought about at the time of awakening by the increased discharge of water and carbon dioxide. Pembrey's numerous observations show that a dormouse loses, on an average, less than 1 per cent. of its weight within one and a half hours of the commencement of awakening.⁶

Nor can the result be attributed to an arrest of purine destruction at the time of awaking. If such arrest is to explain the increase of purine nitrogen from, presumably, 0.08 per cent. to 0.105 per cent. within two hours of arousal, the hibernating animal must have been converting into non-purine compounds at least 15 per cent. of its purines per hour; in view of the fasting condition and greatly reduced respiratory exchange in hibernation this seems altogether unlikely. The increased amount of purines appears, then, to be due to a synthesis of these compounds during the return of the animal to the active state.

* At this time there was a sufficient number available to allow of the selection of series having the same total weight

As the increase observed is brought about within one or two hours, some or all of the newly formed purine is presumably at this time in a free state. An attempt was made in the first analysis to estimate the free and combined purines separately,⁹ but the method of separation did not appear satisfactory.

It is possible that the additional amount of purines in the body plays a part in stimulating the production of heat. The administration of xanthin and caffein by the mouth produces a rise of body temperature.¹⁰

The estimations recorded here give, of course, no indication as to the tissue in which the formation of purines occurs. The heat liberated at the time of awaking is held by most workers on hibernation to come chiefly from the muscles,¹¹ and there is some evidence that muscle is capable of synthesising purine compounds. This evidence may be summarised as follows:—(1) Adult muscle differs from other tissues in containing a percentage of hypoxanthin which is very large in proportion to the amounts of adenin and guanin present;¹² this is true even of animals (e.g., the dog) in which the muscles contain no adenase;¹³ (2) the perfused hind limbs of the dog eliminate uric acid continuously while maintaining a constant purine base content.¹⁴

SUMMARY

Dormice when awaking from hibernation were found to contain 30 per cent. more purine nitrogen than was present before or during hibernation. The results indicate that a synthesis of purines takes place at the time of awakening.

The expenses of this work were met by a grant from the Science Committee of the British Medical Association.

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