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THE ACTION OF DINITROPHENOL AND INSULIN IN ACCELERATING THE METABOLISM OF ETHYL ALCOHOL¹

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The value, on occasion, of accelerating the removal of alcohol from the body, especially in cases of acute alcoholic intoxication, is so evident as to require no elaboration. However, the amount which can be eliminated by the ordinary excretory channels is so small as to be practically insignificant, and the rate of metabolism of alcohol in the body is peculiarly resistant to modification, proceeding at a constant rate (1, 2, 3) for the individual. In spite of the popular sobering effect of a brisk walk in the cold air, it has been shown experimentally that neither external cold (4) nor muscular exercise (5, 6, 7) exerts the slightest influence on this constant rate of metabolism.

Nevertheless, two substances, dinitrophenol and insulin, have been demonstrated to accelerate the speed of combustion of alcohol in experimental animals. It was shown by Supniewski (8) that the simultaneous administration of a unit of insulin per kilogram with the dose of alcohol in rabbits caused twice as rapid a fall of blood alcohol as in controls which did not receive insulin. Insulin is also known to increase the acetaldehyde concentration of the blood (8), and acetaldehyde may be one of the intermediary products in the metabolism of alcohol. Widmark (9) has shown that the administration of 10 mgm. per kilogram of dinitrophenol to dogs which have received a dose of alcohol is effective in more than doubling the rate of disappearance of alcohol from the blood. He feels that at least a part of this increase may be due to hyperventilation and hyperthermia which accompany the dose employed. This work has been confirmed by Harger and Hulpieu (10).

It has been the purpose of the present work to ascertain the value of these agents in the practi-

cal therapeutics of alcohol intoxication in man. To this end, we have subjected them to experimental trial both in vitro and in vivo, always bearing in mind that the dosage used must be within the limits prescribed by safety in administration to man.

EXPERIMENTAL WORK

The action of dinitrophenol in accelerating the metabolism of alcohol by rat liver in vitro has already been reported by us (11). Suffice it to say that concentrations of from 1:5,000,000 to 1:20,000,000 were shown to increase the amount of .1 per cent alcohol metabolized by a fixed amount of rat liver from 5 to 10 per cent. Higher concentrations showed no effect or slight inhibition. In the absence of animal tissue, dinitrophenol was not effective in causing a disappearance of alcohol from the solution.

In vivo, two approaches were made to the problem. Firstly, a test dose of .5 cc. ethyl alcohol was administered to a subject, and the rate of fall of the alcohol content of the blood followed at intervals. Subsequently, the subject was given 100 mgm. dinitrophenol three times daily for a period of two weeks, during which time there was an increase of 30 per cent in her basal metabolic rate. In spite of this, on the administration of a similar test dose the rate of fall of the blood alcohol was found to be identical with the first trial.

Secondly, another subject was given 1.5 cc. of alcohol per kilogram as a 20 per cent solution in normal saline in one hour, the intravenous route being again employed. An hour was allowed to elapse for equilibration between the blood and tissues, and then the rate of decline of the blood alcohol followed at hourly intervals for two hours, at the end of which time 500 mgm. of dinitrophenol were administered by mouth, and the blood alcohol again determined at hourly in-

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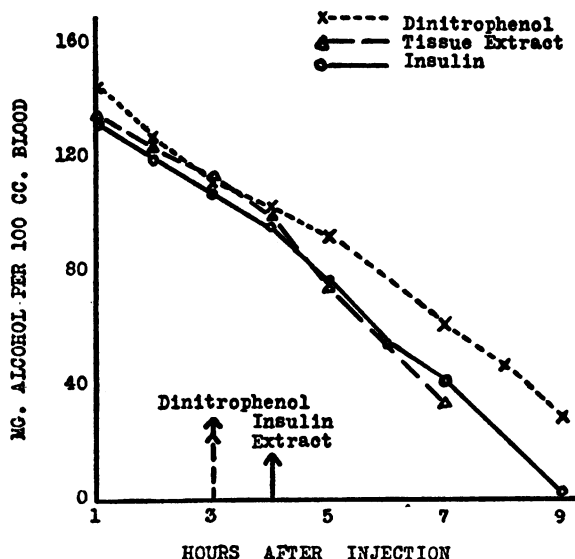


FIG. 1. THE INFLUENCE OF DINITROPHENOL, INSULIN, AND INSULIN-FREE PANCREATIC EXTRACT ON THE CURVE OF BLOOD ALCOHOL CONCENTRATION FOLLOWING ADMINISTRATION OF A TEST DOSE OF ALCOHOL INTRAVENOUSLY.

tervals. The results are shown in Figure 1, and tabulated in Table I. No rise in body temperature, or noticeable increase in respiration, was observed with this dose, which is, however, as high as could be routinely administered to man with safety.

TABLE I

Increase in rate of metabolism of alcohol in man

Accelerator	Average decline before administration	Average decline after administration	Increase
	<i>mgm. per 100 cc. per hour</i>	<i>mgm. per 100 cc. per hour</i>	<i>per cent</i>
Dinitrophenol, 500 milligrams.....	13.7	14.4	5
Insulin, 1 unit per kilogram.....	11.7	18.0	54
Insulin, 1 unit per kilogram.....	14.3	20.0	40
Tissue extract, 10 cc.....	11.3	18.6	65
Tissue extract, 10 cc.....	14.3	16.7	17

With insulin, the same technic in vitro was employed as with dinitrophenol. Three hundred milligrams of rat liver, sliced to a thickness of .5 mm., were placed in a 25 cc. Erlenmeyer flask, 3 cc. of approximately .1 per cent alcohol in phos-

phate buffer at pH 7.4 and sufficient insulin to bring the solution to the desired concentration added, the air replaced by oxygen, and the flask agitated 120 times per minute in an incubator at 37 degrees C. for two hours. At the end of this time the action was stopped by placing the flasks in ice water, and the analyses for alcohol carried out by the method of Cannan and Sulzer (12). The results may be seen in Table II. Controls were run in each case without insulin. All values are the average of duplicate determinations.

TABLE II

Increase in alcohol combustion in vitro

Preparation (3 cc. 0.1 per cent alcohol in buffer pH 7.4 in each)	Increase in alcohol combustion over control <i>mgm. per 100 cc. per hour</i>
Liver and insulin, 1 unit per liter.....	5.0
Liver and insulin, 1 unit per liter.....	2.6
Insulin, 1 unit per liter.....	5.5
Insulin, 1 unit per liter.....	2.7
Insulin, 1 unit per liter.....	2.9
Insulin, 1 unit per liter.....	3.2
Insulin, 1 unit per liter.....	2.2
Tissue extract, 0.5 cc. per liter.....	2.7
Tissue extract, 0.5 cc. per liter.....	1.9

Again a control was run on the same mixture without the presence of the rat liver. Here, in contrast to the inactivity of dinitrophenol, there was a disappearance of alcohol from the solution, which was approximately equal to the increase shown in the above table when insulin was added to the rat liver flasks. The results are seen in Table II.

Thus, commercial insulin under these conditions is capable of causing the disappearance of alcohol. That this is an oxidative process was shown by displacing the air with nitrogen rather than oxygen, in which case no alcohol was destroyed.

Since commercial insulin is, after all, a tissue extract, and tissue extracts have long been known to be effective in causing the oxidation of alcohol (13, 14), we repeated the experiment using an insulin free pancreatic extract (15). Here again some of the alcohol disappeared from solution, as can be seen from Table II.

In the investigation of insulin in vivo, two human subjects were given a test dose of 1.5 cc. of alcohol per kilogram by vein, and after an interval of an hour blood alcohol determinations were run hourly for three hours, at which time 1 unit

of insulin per kilogram was administered hypodermically, the simultaneous administration of 200 grams of glucose in a small amount of water being effected by mouth. Hourly blood samples were analyzed for alcohol subsequent to the injection. At no time did the subjects evidence any of the signs of hypoglycemic shock. Figure 1 shows the acceleration of the decline of the alcohol curve following the administration of insulin in one of the subjects, amounting to a 50 per cent increase in the rate. The increase in rate of metabolism in each case is seen in Table I.

In order to determine if the insulin effect could be produced by the insulin free pancreatic extract, the experiment was repeated, 10 cc. of the extract being given intramuscularly in place of the insulin. The results are tabulated in Table I, and in the case of one of the subjects, shown graphically in Figure 1, show about the same activity as insulin.

SUMMARY

It has been shown that both dinitrophenol and the two pancreatic extracts are capable of increasing the rate of metabolism of alcohol by rat liver in vitro. Insulin and insulin-free pancreatic extract, unlike dinitrophenol, are effective in causing the oxidation of alcohol in the absence of animal tissue.

In vivo, dinitrophenol was not effective in appreciably increasing the rate of oxidation of alcohol in the maximum dose deemed safe for routine administration in man. Insulin, however, in a dose of 1 unit per kilogram, is effective in producing a fifty per cent increase in the rate of disappearance of alcohol from the blood stream. When administered with the appropriate amount of glucose, this dosage may be used safely. That the action may not be due to insulin itself, but to some other component of the commercial product, is shown by the similar effect demonstrated with the insulin-free pancreatic extract. Indeed, it would be very unlikely that a substance such as insulin, with its highly specific action, should also be a factor in alcohol metabolism. Much more probable is the presence in pancreatic extract, and perhaps in the extracts of other organs, of a principle capable of effecting the combustion of alcohol. The isolation of this principle from the other components of tissue extracts, and its con-

centration, may give us a preparation of value in acute alcoholic intoxication. Further work in this direction is in progress.

CONCLUSIONS

1. Dinitrophenol accelerates the metabolism of alcohol by animal tissues, in vitro.
2. Insulin and insulin-free pancreatic extract effect the oxidation of alcohol in vitro in the absence of tissue.
3. Dinitrophenol is not an effective accelerator of alcohol metabolism in safe doses in man.
4. Insulin and insulin-free pancreatic extract are capable of increasing the rate of alcohol metabolism approximately fifty per cent in therapeutic doses in man.
5. Isolation of the principle responsible for this action may yield a useful accelerator of alcohol metabolism free from undesirable side-actions.

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