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Effect of Dinitrophenol on Oxidation of Tissues.

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The marked acceleration of metabolism of animals injected with small quantities of dinitro α naphthol reported by Heymans and Bouchaert,¹ Van Uytvanck,² and Euler,³ and a similar action of dinitrophenol observed by Magne, Mayer and Plantefol⁴ and by Tainter and Cutting,⁵ make it of interest to learn whether these substances affect the rate of respiration of isolated tissues and cell suspensions *in vitro*. If that be the case, it may be hoped that a study of the action of these substances will aid in elucidating the mechanism of cellular oxidation and metabolism. We have studied the effect of 2-4 dinitrophenol on the respiration and anaerobic fermentation of yeast and of frog tissues, using Warburg vessels. With muscle, lactic acid was also determined chemically.

Dinitrophenol added to the solutions in which the tissues or yeast are suspended, in concentrations of the same order as perhaps exists in the tissue fluids after administration of toxic or even large therapeutic doses to man or animals, causes a marked increase of respiration of tissues so far examined. With increasing concentrations, the effect rises to a maximum beyond which the rate of respiration is progressively decreased. The optimum for frog tissues at 25° pH 7.5 is 0.5 mg. % and for yeast at 30° pH 4.5 0.36 mg. %.

The effect is most marked with frog muscle, the resting respiration of which is raised about 8 times above the normal, or to a level somewhat above that observed in similar muscles after maximum stimulation or even hashing. The marked increase caused by dinitrophenol is not accompanied by twitching, and the muscle remains irritable for at least 3 hours. A marked acceleration of anaerobic lactate production is caused by dinitrophenol, and reaches levels

¹ Heymans, C., and Bouchaert, J. J., *Comp. rend. Soc. Biol.*, 1928, **99**, 636; *Arch. Inter. Pharm. et de Ther.*, 1928, **35**, 63.

² Van Uytvanck, P., *Comp. rend. Soc. Biol.*, 1930, **103**, 29; *Arch. Intern. Pharm. et de Ther.*, 1931, **41**, 160.

³ Von Euler, U. S., *Comp. rend. Soc. Biol.*, 1931, **108**, 249; *Arch. Intern. Pharm. et de Ther.*, 1932, **43**, 67.

⁴ Magne, H., Mayer, L., and Plantefol, L., *Ann. de physiol.*, 1932, **8**, 1.

⁵ Tainter, M. L., and Cutting, W. C., *PROC. SOC. EXP. BIOL. AND MED.*, 1932, **29**, 1268.

observed with hashed muscle. The controlling factor of lactic acid production present in normal muscle appears to be removed by the action of dinitrophenol and the process of glycolysis proceeds at nearly the maximum rate. In normal muscle at rest there is no aerobic glycolysis, but in the treated muscles there is an accumulation of lactic acid in spite of the high O_2 consumption. A part of the acceleration in O_2 consumption may therefore be explained by the increase in lactic acid.

With kidney an increase in O_2 consumption of 75% was found, with liver 30% and with nerve 45%.

Dinitrophenol causes an acceleration of 50% in the rate of the oxygen consumption by yeast with glucose as substrate. Chemical analysis of the glucose lost during respiration shows an accelerated utilization. The oxygen consumed by normal yeast accounts for the complete oxidation of 33 to 40% of the glucose which disappears, while in yeast treated with dinitrophenol 70 to 75% of the glucose lost is accounted for by the O_2 consumed. This suggests the inhibition of some other process by which yeast normally disposes of a part of the glucose consumed.

While the rate of anaerobic fermentation by yeast is unaffected (Cutting and Tainter⁶), the total CO_2 produced is increased by dinitrophenol. Instead of the normal 75 to 80% of the theoretical CO_2 from a given amount of sugar, 85 to 90% is formed by treated yeast. Aerobic fermentation, low in normal yeast, is somewhat accelerated in treated yeast, and the rapid oxidation rate continues after the glucose has disappeared; the products of oxidation are the fuel, since the yeast finally returns to the low rate for normal yeast. Dinitrophenol has only slight effect on the respiration of yeast in the absence of added substrate. When the fermentation and oxidation of glucose by yeast is inhibited by iodo-acetate, the addition of dinitrophenol causes no rise in respiration.

⁶ Cutting, W. C., and Tainter, M. L., *J. Pharm. and Exp. Ther.*, 1933, **48**, 410.