In vitro Inhibition of Anaerobic Glycolysis by Phenothiazine Ataractic Drugs

Although a variety of enzymatic effects have been demonstrated with chlorpromazine and related phenothiazine derivatives, relatively little attention has been given to the effect of such compounds on anaerobic glycolysis. BERNSOHN, NAMAJUSKA, and COCHRANE reported that rat brain hexokinase activity was inhibited markedly by 10^{-3} *M* chlorpromazine but that the anaerobic glycolytic activity of fortified rat brain homogenates was not altered by this rather high concentration of the drug[1]. More recently, MORACZEWSKI and DU BOIS found that the same concentration of chlorpromazine had no effect on anaerobic glycolysis in rat or mouse liver homogenates and that a single, massive dose of the drug did not reduce the glycolytic activity of mouse liver slices[2]. In addition, these workers demonstrated slight inhibition of glycolysis in rat and mouse liver homogenates by 10^{-3} *M* chlorpromazine sulfoxide. Studies in this laboratory have shown that several phenothiazines, including chlorpromazine, are capable of inhibiting anaerobic glycolysis in rat brain homogenates provided that the incubation time is extended beyond the 30–40-min periods employed by BERNSOHN *et al.* and MORACZEWSKI and DU BOIS.

The results presented in the Table show that while 10^{-5} *M* chlorpromazine has no effect on glycolysis in rat brain homogenates, 10^{-3} *M* concentrations of the drug produce a striking effect after 1 h. Essentially identical results were observed with two other phenothiazine ataractic agents, promazine and mepazine. From a consideration of the structures of these three drugs it can be inferred that neither the 2-chloro substitution nor the N-(3'-dimethylaminopropyl) of chlorpromazine moiety is essential for inhibition of anaerobic glycolysis by phenothiazines.

Inhibition of Anaerobic Glycolysis in Rat Brain Homogenates by Chlorpromazine

System	Glucose added	$Q_{CO_2}^{N_2}$		
		1 h	2 h	3 h
Endogenous . .	—	1·99±0.64	0·99±0·41	0·90±0·19
Control	+	5·32±0·61	3·48±0·83	3·46±0·41
Chlorpromazine, 10^{-5} *M*	+	5·70	2·70	3·30
Chlorpromazine, 10^{-3} *M*	+	4·60	1·66	1·70

This finding, together with the positive results reported by BERNSOHN *et al.*[1] and MORACZEWSKI and DU BOIS[2], suggest that phenothiazines may be converted slowly under anaerobic conditions, more rapidly in the presence of oxygen, to metabolic products which arec apable of inhibiting anaerobic glycolysis, possibly through altering the rate of the hexokinase reaction. The fact that high concentrations of chlorpromazine are required to bring about this effect could be ascribed to the quantitative aspects of this postulated metabolic pathway, or perhaps interpreted as being related to the toxic rather than the therapeutic mechanism of action of the drug.

Conditions

Normal, male albino rats were decapitated, the brains removed and the cerebral cortex homogenized immediately in a Potter-Elvehjem grinder in 4 parts of ice-cold Krebs-Ringer bicarbonate buffer[3]. To the main compartment of standard Warburg flasks, containing 2·3 ml of buffer or a glucose-buffer solution, was added 0·7 ml of homogenate (about 33 mg dry weight). The compounds to be studied[4] were dissolved in the glucose-buffer solution and added to give a final concentration of 10^{-5} *M* or 10^{-3} *M*. Where present, the final concentration of glucose was 0·2%.

All flasks were gassed with N_2–CO_2 (95%–5%) and equilibrated to 38°C over a 20-min period. Measurements of gas production were made at 15 min intervals and results expressed in terms of $Q_{CO_2}^{N_2}$ (µl CO_2/mg dry weight/h) calculated over the indicated periods. Data reported are averages of 12 determinations ± one standard deviation ('endogenous' and 'controls' systems) or averages of two experiments ('chlorpromazine' systems).

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Zusammenfassung

Im Gegensatz zu Feststellungen anderer Forscher hemmten Chlorpromazin und zwei strukturell verwandte ataraktisch wirkende Phenothiazinderivate die anaerobe Glykolyse von homogenisiertem Rattenhirn. Der Nachweis dieser Hemmung bedarf einer längeren Inkubation, was auf die Mitwirkung eines zeitbedingten Vorgangs, wie metabolische Umwandlung der Phenothiazine in Hemmstoffe, deutet.

[1] J. BERNSOHN, I. NAMAJUSKA, and L. S. G. COCHRANE, Arch. Biochem. Biophys. *62*, 274 (1956).

[2] A. S. MORACZEWSKI and K. P. DU BOIS, Arch. int. Pharmacodyn. *120*, 201 (1959).

[3] W. W. UMBREIT, R. H. BURIS, and J. F. STAUFFER, *Manometric Techniques and Tissue Metabolism* (2nd Edition, Burgess Publishing Co., Minneapolis 1949), p. 119.

[4] Chlorpromazine was obtained from Smith, Kline and French Laboratories, Philadelphia, mepazine from Warner-Chilcott Laboratories, Morris Plains, New Jersey, and promazine from Wyeth Laboratories, Inc., Philadelphia.

Aufhebung der Knospenruhe von Reben durch Rindite

Die Knospenruhe der Reben erreicht in den Monaten September bis November ihre grösste Tiefe. Durch eine Kältebehandlung ist sie nicht zu verkürzen, während Gibberellinsäure je nach Sorte und Zeitpunkt der Behandlung austriebshemmend wirkt[1]. Es wurde darum versucht, die Knospenruhe durch Behandlung mit dem von DENNY[2] an Kartoffelknollen entwickelten, austriebsfördernden Gemisch von Äthylenchlorhydrin, Äthylendichlorid und Tetrachlorkohlenstoff (Volumenverhältnis 7:3:1), das als Rindite bekannt ist, zu brechen, da dieses Substanzgemisch bereits mehrfach erfolgreich zur Aufhebung der Samenruhe[3,4] und auch vereinzelt zur Förderung des Austriebes ruhender Winterknospen[5] verwendet wurde.

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[3] I. SZALAI, Acta agron. Acad. Sci. hungaricae *7*, 25 (1957).

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[5] S. THORUP, Physiol. Plantarum *10*, 728 (1957).