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Metabolic inhibition in primary cell cultures by lipid-soluble molecules

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A range of lipid soluble molecules have been found to cause metabolic inhibition of monkey kidney (MK) epithelial cells in culture. The most detailed studies have been performed on butylated hydroxytoluene (BHT). At concentrations up to 0·136 mM BHT there were no visible cytopathological effects in the MK cells examined by phase contrast microscopy. However, this dose inhibited the rate of MK cell growth as indicated by mitotic indices and cell counts. Within 30 min of exposure there was a decrease in DNA, RNA and protein synthesis with a similar time course for each component, suggesting that the inhibition is non-specific in this respect. The inhibition is fully reversible (Milner, 1967).

A range of chemically dissimilar structures produce the same type of metabolic inhibition as BHT at concentrations related to their lipid solubilities. These results support the conclusion that the inhibitory effect is caused by a non-specific mechanism which depends primarily on the concentration of the perturbing agent within a hydrophobic cellular environment.

An obvious candidate is the cell membrane, and we have taken as a working hypothesis that the cellular metabolism is depressed by structural perturbation of the cell membranes in the presence of lipid-soluble molecules.

The data bear a strong resemblance to the relationship of anaesthetic potency to the oil/water partition coefficient first demonstrated by Overton & Meyer. Seeman (1966) has also established that anaesthetic potency is related to the stabilization of the erythrocyte membrane against hypotonic haemolysis over a very wide concentration range ($>10^6$). This suggested a model system to test our hypothesis for inhibitory activity, and we have shown that the ability of lipid-soluble molecules to inhibit MK cell metabolism is directly correlated with the ability to stabilize the erythrocyte membrane. We conclude that the inhibition of cell metabolism, as well as anaesthetic activity, is determined primarily by the concentration of lipid-soluble agent in the membrane, and is not greatly dependent on chemical structure.

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Destruction of chlorpromazine during absorption by rat intestine *in vitro*

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It is commonly supposed that orally administered chlorpromazine is rapidly and well absorbed in man, although there appears to have been no systematic investigation of the absorption phenomenon (Goodman & Gilman, 1965; Shepherd, Lader & Rodnight, 1968). Doubt was recently cast on the supposition by measurements of unchanged chlorpromazine in plasma of man and animals (Curry, Davis, Janowsky & Marshall, 1970; Hollister, Curry, Derr & Kanter, 1970; Curry, Derr, Maling & Williams, 1970); concentrations of unchanged drug in plasma after injected doses were 3–10 times higher than those after oral doses during the 48 h following administration. This indicated *incomplete* absorption of oral doses as unchanged drug. In contrast, concentrations of metabolites of chlorpromazine in urine after doses by the two routes were similar. This indicated *complete* absorption, either as unchanged drug as or metabolites. We therefore investigated the possibility that the drug could be converted to absorbable metabolites during the process of absorption.

Krebs bicarbonate fluid containing ^{35}S-chlorpromazine (50, 100 and 200 μg/ml) was circulated at 37° C through the lumen of rat isolated intestine. The serosal surface was bathed with a similar solution containing no chlorpromazine (technique of Fisher & Parsons, 1949). Unchanged chlorpromazine, measured by gas chromatography, disappeared rapidly from the luminal solution and was partially transferred to the serosal solution and partially retained in the intestinal wall. Concentrations of total radioactivity and of unchanged chlorpromazine were similar both in the luminal solution and in the intestinal wall. In contrast, radioactivity appeared in the serosal solution more rapidly than did unchanged chlorpromazine; at the end of the experiment (60 min), 15–32% of the serosal radioactivity was present as unchanged drug.

These observations indicated that chlorpromazine was decomposed during absorption *in vitro*. The mechanism of this decomposition is not clear, but results of control experiments demonstrated that chemical decomposition unrelated to the presence of intestinal material did not occur. Biochemical decomposition may have been brought about by intestinal flora or enzymes in the intestinal wall. If this process were to occur *in vivo* it might be the cause of concentrations of unchanged drug in plasma being less after oral doses than after injected doses.

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