The use of pH 7.4 provided a basis for comparisons with biological data. In general, occurrence of groups which are introduced metabolically *in vivo* led to increased hydrophilic character.

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Some effects of chlorpromazine on oxidative phosphorylation in synaptosomes from rat brain

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Several workers have investigated the effect of phenothiazine derivatives on metabolic processes in the CNS (Guth & Sprites, 1964). However, the purpose of this study was to investigate the effects of chlorpromazine on oxidative phosphorylation in synaptosomal preparations. Synaptosomes were prepared from a 10,000 *g* pellet on a discontinuous sucrose gradient based on a method by Marchbanks & Whittaker (1967). Respiratory activities were measured with an oxygen electrode as described by Verity (1972), using succinate, glutamate, malate, α-glycerophosphate, ascorbate and DPNH as substrates. The effects of 10^{-5} to 10^{-3} M chlorpromazine on state 3 respiration were investigated, and succinic dehydrogenase activity was measured spectrophotometrically by the dichlorophenolindophenol, sodium neotetrazolium reductase, cytochrome *c* reductase and potassium ferricyanide methods.

The only substrate to show any significant inhibition of oxygen uptake by chlorpromazine was succinate which gave an ID_{50} of 3.1×10^{-4} M. There was some slight inhibition of glutamate oxidation but this was only about half that of succinate inhibition and it was not possible to calculate an ID_{50} for this substrate. None of the other substrates showed any inhibition using concentrations of up to 10^{-3} M chlorpromazine. There was some indication that, in the presence of high concentrations of chlorpromazine in preparations of synaptosomes more than 3 h old, damage to the membrane may have occurred. Studies on brain and liver mitochondria prepared in a similar manner to synaptosomes indicated that, in the concentration ranges of chlorpromazine used, there was only 20% inhibition of succinate compared to that found for synaptosomes.

Studies using 2-3 ^{14}C-succinate showed no inhibition of the uptake of succinate into synaptosomes by chlorpromazine concentrations capable of producing 80% inhibition of respiration. Furthermore, studies on the swelling of synaptosomes indicated that, in all probability, the uptake of succinate was a slow process.

In order to investigate whether chlorpromazine was exerting its effects on the cytochromes, experiments were done using ascorbate as a substrate, which feeds in at the end of the electron transport chain, but no inhibition for this substrate could be detected. These findings were confirmed by spectrophotometric studies. Other experiments showed that the observed effect was not via DPNH nor the uptake of succinate. The effects of chlorpromazine on succinic dehydrogenase was therefore studied in a variety of assay systems. Using the four assay systems already described, no inhibition of synaptosomal succinic dehydrogenase could be detected. Effects of chlorpromazine on FAD were examined by spectrophotometric and chromatographic methods but no definite conclusions can be drawn from these studies.

It would, therefore, appear that chlorpromazine affects the metabolic processes of synaptosomes through inhibition of succinate oxidation, but the exact mechanism of this inhibition is not yet clear.

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