The effect of cetyltrimethylammonium on the uptake of sodium, sucrose, and albumin by frog sciatic nerves*

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PROLONGED exposure of frog sciatic nerves to cetyltrimethylammonium bromide (CTMB) and other ionic surface-active agents leads to an irreversible block of axonal conduction.[1, 2] Perhaps more remarkable than the blocking action, *per se*, is the observation that pretreatment with ionic surfactants renders the surviving constituent fibers of frog nerve susceptible to reversible conduction block by externally applied curare, neostigmine, and acetylcholine;[2–4] these latter compounds are normally active only at junctional regions such as the neuromuscular complex. Rosenberg and Ehrenpreis have also reported reversible conduction block by externally applied curare in CTMB-pretreated squid giant axons.[5] To explain the foregoing a hypothesis was proposed which stated that CTMB and other ionic surfactants disrupt or disperse the various permeability barriers in a nerve trunk—thus increasing the penetrability of externally applied agents. Eventually the plasma membranes of constituent fibers are structurally disorganized, and it is this terminal phase that probably underlies the irreversible conduction block.[2, 3, 6]

Experimental evaluation of a number of predictions should reveal whether or not the above hypothesis bears any kinship to the realities of the action of surfactants on nerves. This report is concerned with one such prediction; if the effectiveness and/or totality of permeability barriers is actually reduced then the uptake of certain substances should be increased subsequent to surfactant treatment. Two of the substances employed are normally restrained to the extracellular spaces, sucrose, and albumin. The third substance, sodium, is largely, though not wholly, confined to the interstitial regions.

Standard uptake procedures were followed. Freshly excised frog sciatic nerves were incubated for 60 min in buffered frog Ringer's solution (BFR) or in surfactant solution containing 1·0 mmoles CTMB/L of BFR. After this all nerves were washed with fresh BFR, containing no surfactant, for 15 min. The nerves were then placed in incubating chambers containing BFR which contained a small amount of ^{22}Na for the sodium-uptake series, ^{14}C- sucrose for the sucrose series, or radio-iodinated serum albumin (RISA) for the albumin series. After 2 hr, each nerve was quickly removed from its incubating medium, washed, blotted, weighed, and spread onto a counting planchet. After thorough dehydration its dry weight was determined and its content of ^{22}Na, sucrose, or RISA assayed radiometrically. Several aliquots of the incubating media were also assayed. The final result was expressed as an uptake fraction—the ratio of the counts per gram of tissue water to the counts per milliliter of incubating medium.

TABLE 1. UPTAKE OF SODIUM, SUCROSE, AND ALBUMIN BY FROG SCIATIC NERVES*

	Counts/gram tissue H_2O / Counts/ml external medium ± S.D.		
Experimental group	$^{22}NaCl$	^{14}C-Sucrose	$R^{131}ISA$
Normal control	0·379 ± 0·037	0·135 ± 0·012	0·142 ± 0·024
CTMB (10^{-3} M)	0·605 ± 0·027	0·193 ± 0·019	0·286 ± 0·041

* Values are the means of a minimum of 17 nerves in each series.

The results are summarized in Table 1 which gives the means of the uptake values for each experimental series. The data show a significant and dramatic increase in uptake by CTMB-pretreated nerves. Relative to the controls, the increased uptake is 60 per cent for sodium, 43 per cent for sucrose, and 101 per cent for albumin. It has been reported that similar treatment of frog sciatic nerves

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(60 min in 1·0 mmoles CTMB/L BFR) renders the surviving constituent fibers susceptible to reversible block by curare, neostigmine, and acetylcholine.[2-4] For example, after the CTMB pretreatment, 4×10^{-4} M neostigmine effects about a 73 per cent reduction of the A-potential in 30 min.[2] Though certainly not proving the original hypothesis, the uptake data reported here are in excellent agreement with the concept that ionic surfactants diminish permeability barriers and thus enhance the uptake of substances that are normally constrained to the extracellular spaces.

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Charge transfer, hydrogen bonding and drug action

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THE recent work of Lyons and Mackie on the electron-donating properties of reserpine and the phenothiazine tranquillizers[1] raises once again the question of a possible causative relation between charge transfer and drug action. As they pointed out, an immediate difficulty is that phenothiazine itself is not a tranquillizer, although it is just as strong an electron donor as its active derivatives. This note is intended to show how the original suggestion regarding charge transfer and drug action[2] can be preserved, by combining it with one of the classical postulates, i.e. hydrogen bonding.

We suggest that specific drug activity can result when a strong electron-donor or -acceptor molecule is provided with a side-chain capable of hydrogen bonding in the appropriate sense. Besides helping to anchor the drug to its substrate, the hydrogen bond is postulated to activate the substrate towards electron transfer in the complementary direction; in this way a simple irritant or fungicide can become a true drug (phenothiazine itself has anthelmintic properties). This suggestion is based on the fact that acridine becomes a strong electron acceptor in the presence of weak acids, the experimental conditions favouring hydrogen bonding rather than ionization.[3]

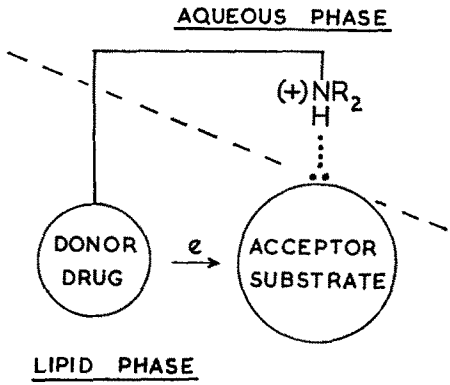

FIG. 1.