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This Week's Citation Classic

Seeman P. The membrane actions of anesthetics and tranquilizers. *Pharmacol. Rev.* **24:**583-655, 1972. [Pharmacology Department, University of Toronto, Canada]

This review integrated data to create the concept that membranes are expanded and fluidized by lipid-soluble drugs, altering many membrane functions. These nonspecific anesthetic-like effects occur whenever the drug is approximately ten millimolar *in the membrane phase,* **a value obtained directly from the drug's partition coefficient. This rule helps to distinguish between receptor and non-receptor mechanisms for membrane-active drugs. [The** *SCI*® **indicates that this paper has been cited in over 1,300 publications since 1972.]**

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" 'How does one decide whether a membrane-active drug acts specifically on receptors or nonspecifically on the membrane? For instance, do tranquilizers (now called neuroleptics) or all anesthetics act on receptors or do they act nonspecifically to depress membrane excitability indirectly?' These questions preoccupied me while I was a graduate student at Rockefeller University in New York City between 1961 and 1966 My wife, Mary, was at that time a psychiatric resident at Manhattan State Hospital, working with many patients whose diagnosis was schizophrenia This was my motivation to try to understand the molecular mechanism for the antipsychotic action of neuroleptic drugs. I felt that, if I could understand how the drugs exerted their effects, it would provide me with a research strategy for studying the presumably abnormal brain chemistry of schizophrenia. I first wanted to determine whether the site of neuroleptic action was specific or nonspecific. Knowing this, I could then go on to study it in the mentally disordered brain.

"I started by testing the effects of neuroleptics on erythrocyte membranes. As had been previously noted by others,[1] these drugs inhibited hemolysis. I soon found that virtually all lipid-soluble drugs, including anesthetics, alcohols, etc., protected erythrocytes from osmotic hemolysis by expanding the area of the membrane by only one to two percent.

"Membrane expansion of the kind I found should theoretically loosen, fluidize, or disorder the membrane constituents. Such an alcohol-induced fluidization of the membrane was discovered by Jim Metcalfe, Arnold Burgen, and myself[2] when I was a postdoctoral fellow at the University of Cambridge in 1966.

"Returning to Canada in 1967, I started measuring the binding of radioactive neuroleptics and anesthetics to membranes in order to establish a relation between membrane effect and membrane occupancy by the drug. Working with Wim Kwant and Sheldon Roth, we found that these and other lipid-soluble drugs all expanded and fluidized membranes whenever the drug attained a molarity *within the membrane phase* of about ten millimolar This universal rule had been predicted by Meyer and Overton in 1901.[3,4] They had worked with olive oil as a model for the membrane.

"Since most biologists use lipid-soluble drugs on their systems, this review article has served as a convenient reference on the molecular mechanisms for the nonspecific membrane actions of anesthetics and other lipid-soluble drugs. The importance of the review is that it correlates the membrane effects with drug concentrations. This entailed a lengthy and detailed examination of the anesthesia literature since 1896, a voluminous task done on weekends amidst ice hockey and touch football with my three sons. The further-reaching importance is that the review prompted the subsequent discovery that alcohol-tolerant tissues have membranes which are more resistant to fluidization by ethanol.[5,6]

"The review shows how to calculate the membrane concentration for a particular drug from the partition coefficient. If the drug is membrane-active at much less than ten millimolar *within the membrane,* then a specific membrane receptor mechanism must be postulated. It was this result which subsequently led me to determine directly that dopamine receptors were the primary sites of neuroleptic action. "[7]

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