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THE MEMBRANE VOLUME OCCUPIED BY ANESTHETIC MOLECULES: A REINTERPRETATION OF THE ERYTHROCYTE EXPANSION DATA

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Summary

Seeman and coworkers (Seeman, P. (1972) Pharmacol. Rev. 24, 583—655) calculated that anesthetic agents expand membrane volume ten times more than the van der Waals volume of the agent alone. Their calculation was based on the assumption that the thickness of the erythrocyte membrane expands at the same rate as the surface area. However, recent data on bilayer membranes demonstrate that an expansion of membrane surface area is accompanied by a decrease in membrane thickness. A reinterpretation of their erythrocyte area expansion data using an appropriate contraction of membrane thickness suggests the volume in a membrane occupied by anesthetic molecules is approximately equal to their van der Waals volume.

In a thorough series of studies Seeman and coworkers demonstrated that clinically-used concentrations of general and local anesthetic agents expand erythrocyte membrane surface area by 0.4 and 2%, respectively. "Assuming uniform swelling in all directions" they calculated a membrane volume increase of 0.6 and 3.5%, respectively. For both types of anesthetic agents the increase in membrane volume thus calculated was found to be ten times the van der Waals volume of the anesthetic molecules dissolved in the membrane [1].

Seeman et al. have presented several possible mechanisms for the 10-fold volume increase [1]. This volume enhancement has been widely quoted as evidence for and against various molecular models of anesthesia [2]. The question of what occupies the additional 90% of membrane volume has become one of the mysteries of anesthesia theory.

Recent theoretical [3—6] and experimental [4—9] research on membrane structure has demonstrated that when a phospholipid bilayer membrane expands in surface area, it contracts in thickness. This is opposite to the earlier

supposition of Seeman et al. [1] and suggests that volume increase may not be considered to be a 3/2 power of surface expansion. As the surface area of a phospholipid bilayer membrane expands, the conformational mobility of each fatty acid chain is increased. Increased numbers of gauche conformations, or kinks, occur in each chain. Each kink causes a decrease in the length of the fatty acid chain and thus a decrease in overall bilayer thickness [6]. A decrease in bilayer thickness co-incident with surface area expansion induced by a thermal phase transition has been demonstrated in the cell membrane of *Mycoplasma laidlawii* [9] as well as in dipalmitoyl phosphatidylcholine bilayers [5—8]. The resulting small volume increase has been confirmed by experiments on pressure-induced phase transitions [10]. Anesthetic agents have been shown to cause the same kind of surface area-expanding and thickness-contracting phase transitions as are caused by temperature increases [11—14].

Unfortunately the appropriate X-ray data of area versus thickness for the protein-rich erythrocyte membrane are not available for an exact calculation of the volume increase associated with the measured surface area expansion. However, an approximation may be made by noting that a 1.4% volume expansion of a dipalmitoyl phosphatidylcholine bilayer was measured [4] under conditions where the surface area was increased by 21% [5—7]. The same ratio of volume to area change applied to the surface area expansion data of Seeman [1] would yield membrane volume expansions of 0.026 and 0.13% for clinically-used concentrations of general and local anesthetic agents, respectively. Within the limits of error of the X-ray data and the membrane concentration data, these values are equal to the van der Waals volumes of the anesthetics estimated by Seeman to be 0.02 and 0.4% of membrane volume, respectively [1]. This reinterpretation invalidates an argument frequently used against those theories of anesthesia which include phospholipid bilayers as a primary site of action.

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