EVIDENCE FOR IONIC PORES IN EXCITABLE MEMBRANES

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Membranes of excitable cells undergo rapid changes of permeability, which result in brief but intense ion fluxes. A question of long standing is how ions pass through the membrane, which is an insulator. The two major possibilities are that ions are solubilized in the membrane by combination with specialized carrier molecules; or they pass through by way of hydrophilic pores. There is now strong evidence that passive transport of K^+ (and Na^+) in excitable membranes is accomplished by pores. The following is a summary of this evidence.

(*i*) Tetraethylammonium ion and derivatives such as nonyltriethylammonium ion (C_9^+) block the K channels of squid axon provided (*a*) that the ions are in the axoplasm (when externally applied they have no effect), and (*b*) that the K channels are activated by depolarization (Armstrong, 1971). C_9 ions are cleared from the channels at an easily measurable rate on repolarization. The rate of clearing is increased at least six-fold by raising the external K^+ concentration. Other ions, such as Na^+ and Cs^+, when present in the axoplasm also interfere with K ion flow (Bezanilla and Armstrong, 1972). The interference is diminished by external K^+. The mechanism of interference of all these ions and the effect of external K^+ can be easily explained in terms of a pore model. One must postulate that the inner mouth of the pore is not very selective, but accepts K^+, C_9^+, Na^+, Cs^+, or other ions almost indiscriminately; that the pore mouth provides an energy well for the blocking ion, a few kilocalories deep for C_9^+ thanks to hydrophobic interactions, but less deep for the other ions; that the outer portion of the pore is quite selective, and readily accepts K^+ but not the blocking ions, which can enter the mouth but not the remainder of the pore; and finally, that C_9^+, Na^+, or Cs^+ in the mouth block the pore until removed. A K^+ ion entering the pore from outside electrostatically repels, for example, a C_9 ion blocking the pore mouth, and pushes it back into the axoplasm. This effect of external K^+ on the clearing rate of C_9^+ ions from the membrane cannot be explained by any carrier model that I am aware of (see Armstrong, 1975).

(*ii*) The conductance of the passive K transport pathway has been estimated to be about 10^{-12} mho based on the rate of blocking of g_K by TEA^+ or C_9 ion (Armstrong, 1966; 1974). Estimates for the Na conducting units are obtained by dividing sodium conductance per square micrometer of membrane by the number of tetrodotoxin bind-

ing sites per square micrometer. These estimates vary from 10^{-10} to 10^{-12} mho/site. For a driving force of 160 mV, 10^{-12} mho corresponds to a transport rate of 10^6 ions/s. This is almost two orders of magnitude larger than the maximum theoretical transport rate for the carrier nonactin (Läuger, 1972).

(*iii*) A major reason for relatively slow movement of an ion carrier is electrostatic. An ion passing through a lipid membrane in a carrier of reasonable dimensions (5 Å radius) faces an energy barrier of at least 16 kcal/mol, corresponding to a Q_{10} of 2.4 (Parsegian, 1969). For a pore of 5 Å radius, the barrier can be as low as 6 kcal/mol, corresponding to a Q_{10} of about 1.4. The Q_{10} of ion transport through nerve membrane is about 1.2, not far from the Q_{10} of Parsegian's model pore.

(*iv*) The "long pore" effect (Hodgkin and Keynes, 1955) is compatible with a membrane pore, as the name implies. This effect can also be explained with a carrier model (Hodgkin and Keynes, 1955; Horowicz et al., 1968) and the case for a pore rests more strongly on the three preceding arguments.

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