

can account for a fraction of the measured heat, somewhat less than half. The calculations of the energy involve some assumptions and as previously stated the quantitative data obtained from the heat measurements are not very precise so that it may be that revision of the quantities would bring the two into line. However, it is felt that this is not very likely in this case for the following reasons. The calculations of the stored energy both involve an assumed membrane potential of 80 mV which is taken to be a maximum value. It is quite possible that the true membrane potential is only half of this which would reduce the calculated energy to only one quarter of that calculated. It therefore seems that in any revision of the quantities the calculated stored energy is likely to diminish rather than to grow. On the other hand, in the heat measurements themselves most artefacts and possible errors are of the kind which tend to reduce the amount of heat observed so that if the precision of the method improves the most probable outcome would be for the measured heat to be revised upwards rather than the reverse.

For the present, then, we are driven to suppose that there is at least one other major reversible source of heat contributing to the positive and negative phases of the initial heat, along with the free energy stored on the membrane capacitance. The presence of the negative phase of heat absorption is a powerful clue in the search for this extra heat, for in a closed system such as is the nerve on a thermopile during a short interval the presence of cooling is always strongly suggestive of entropy changes. A likely site for such entropy change is in the dielectric of the distributed membrane capacitance. All of the insulating matrix of the membrane is subjected to a stress of about 40 kV/cm by the resting potential. The rapid release and partial reversal of this stress during the action potential can lead to profound reorientation at the molecular level, a process which can be expected to be accompanied by substantial entropy changes. If this insulating layer is regarded as the dielectric of the membrane capacitance then heat will be evolved on discharge if the temperature coefficient of capacitance is positive. The temperature coefficient is not known for small fibres but that of the squid giant axon is indeed positive (Taylor & Chandler 1962) and of such a value that if it held also for the C fibres of the rabbit vagus would lead to an evolution of heat during the rising phase of the action potential some three times greater than the free energy stored on the membrane capacitance.

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Discussion

Thermodynamic analysis of the 'thermal spike'. BY E. NEUMANN (*Max-Planck-Institute of Biophysical Chemistry, D-34 Göttingen-Nikolausberg, Postfach 968, Germany*)

The relatively large heat changes accompanying an action potential (Abbott, Hill & Howarth 1958) may be thermodynamically modelled in terms of cyclic variation of membrane

states. The complex chain of molecular events during a spike may be simplified by the sequence of state changes $A \rightarrow B \rightarrow A$, where A represents the resting stationary state and B symbolizes the transiently excited state of higher ionic permeability.

Under practically isothermal-isobaric conditions, the Gibbs free energy change, ΔG , associated with the process $A \rightleftharpoons B$ is given by

$$\Delta G = \Delta H - T\Delta S, \quad (1)$$

where ΔH is the reaction enthalpy (as heat exchangeable with the environment) and ΔS the reaction entropy.

It has been found that the rising phase of the action potential is accompanied by heat release, Q_{rel} , while during the falling phase heat is reabsorbed, Q_{abs} (Howarth, Keynes & Ritchie 1968).

In the simple A-B model, the first phase is associated with

$$\Delta G_{A \rightarrow B} = \Delta H_{A \rightarrow B} - T\Delta S_{A \rightarrow B},$$

and the second one with

$$\Delta G_{B \rightarrow A} = \Delta H_{B \rightarrow A} - T\Delta S_{B \rightarrow A}.$$

In general, for a cyclic process (where the original state is restored),

$$\Delta G_{A \rightarrow B} + \Delta G_{B \rightarrow A} = 0. \quad (2)$$

In the hypothetical case of ideality (reversibility), $\Delta H = Q$ and $Q_{\text{rel}} + Q_{\text{abs}} = 0$.

Since no *natural* process occurs ideally (i.e. completely reversibly) there are always irreversible contributions. This means a part of $\Delta G_{A \rightarrow B}$ as well as a part of $\Delta G_{B \rightarrow A}$ will dissipate into heat. We may formally split ΔG into a reversible (exchangeable) contribution ΔG^{rev} and an irreversible contribution ΔG^{irr} (Neumann 1973). Thus

$$\Delta G_{A \rightarrow B} = \Delta G_{A \rightarrow B}^{\text{rev}} + \Delta G_{A \rightarrow B}^{\text{irr}},$$

$$\Delta G_{B \rightarrow A} = \Delta G_{B \rightarrow A}^{\text{rev}} + \Delta G_{B \rightarrow A}^{\text{irr}}.$$

By definition $\Delta G^{\text{irr}} = -T\Delta S^{\text{irr}} \leq 0$, since a change in the inner entropy ΔS^{rev} is always larger than or equal to zero (Prigogine 1968).

The measured heats are then given by

$$Q_{\text{rel}} = \Delta H_{A \rightarrow B}^{\text{rev}} + \Delta G_{A \rightarrow B}^{\text{irr}} \quad (\text{negative sign}),$$

$$Q_{\text{abs}} = \Delta H_{B \rightarrow A}^{\text{rev}} + \Delta G_{B \rightarrow A}^{\text{irr}} \quad (\text{positive sign}).$$

Since in a cycle $\Delta H_{A \rightarrow B}^{\text{rev}} + \Delta H_{B \rightarrow A}^{\text{rev}} = 0$, we find for the difference

$$\Delta Q = Q_{\text{rel}} + Q_{\text{abs}} = (\Delta G_{A \rightarrow B}^{\text{irr}} + \Delta G_{B \rightarrow A}^{\text{irr}}) = -T\Delta S^{\text{irr}} \leq 0.$$

This means that due to irreversible contributions $|Q_{\text{rel}}| > |Q_{\text{abs}}|$ (Q_{rel} counting negative!). Experimentally, $|Q_{\text{abs}}| \approx 0.9 |Q_{\text{rel}}|$, [2].

As outlined by Guggenheim (1949), $\Delta G^{\text{irr}} < 0$ or $\Delta F^{\text{irr}} > 0$, *only if phase changes and/or chemical reactions are involved*. Then, for our case we may write

$$\Delta Q = \Delta G^{\text{irr}} = -\sum_j A_j \xi_j < 0,$$

where A is the affinity and ξ is the extent of membrane processes j involved (Neumann 1973).

Evidence is accumulating that at least one contribution to the action potential involves

only a small fraction of the excitable membrane (Cole 1968; Keynes 1970; Fox & Stämpfli 1971). This means that the heat changes Q_{rel} and Q_{abs} are relatively large (Keynes 1970).

Since on the other hand the mutual transition $A \rightarrow B \rightarrow A$ 'readily' occurs, the value of $\Delta G_{A \rightarrow B} = -\Delta G_{B \rightarrow A}$ cannot be very large. In order to compensate a large ΔH (here $\approx Q$), there must be a large value for ΔS ; see equation (1). This means that the *entropy change associated with the membrane permeability change during excitation is also very large.*

It is, in principle, not possible to deduce from heat changes the nature of the processes involved. However, large configurational changes (equivalent to a large overall ΔS) in biological systems frequently arise from conformational changes of macromolecules or macromolecular organizations such as membranes or from chemical reactions. In certain polyelectrolytic systems such changes involve metastable states and irreversible transitions of domain structures (Neumann 1973).

In summary, the large absolute values of Q and the irreversible contribution ΔQ suggest structural changes of the excitable membrane to be associated with the action potential.

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