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Heat production in non-myelinated nerves

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Experiments with the C fibres of the rabbit vagus nerve have established that heat is evolved during the depolarizing phase of the action potential and is absorbed during the repolarizing phase. Subsequent studies using the pike olfactory nerve indicate that the heat production begins at a high rate very early in the depolarizing phase and is completed in advance of the peak of the spike. This would be expected if the heat arises from the energy released by the discharge of the membrane capacitance which varies as the square of the membrane potential; but estimates of the stored energy fall short of the observed heat production by a factor of two or three times. The prominent cooling phase suggests that a substantial part of the heat may arise from an entropy change. Such an entropy change would be expected to result from the change in the electrical stress in the dielectric of the membrane capacitance, and may thus be a manifestation of reversible changes in the molecular architecture of the insulating matrix of the membrane.

It is probable that substantial heat changes accompany the action potential in all nerve membranes but the resulting temperature changes are very small because of the relatively large heat capacity of the axoplasm and inert tissue associated with the nerve trunk. Because of this, the detailed study of thermal events associated with the action potential has been restricted to unmyelinated nerves having fibres of small diameter. In all such nerves studied the heat production is characterized by two distinct phases, first a positive phase of heat production represented by increase of temperature and second, a negative phase or cooling in which almost all of the heat first produced is reabsorbed. These events together constitute the 'initial heat' which is associated directly with the action potential. The difference between the two phases is the residual heat at the end of the action potential and is now referred to as the 'net heat'. In the early studies of nerve heat the instruments used were too slow to distinguish the separate phases and only the difference was observed, so that in the early literature the term 'initial heat' refers to what is now known as the 'net heat'. There is a third phase of heat production, the recovery heat, following after the action potential is over. This is produced at only a low rate but continues for a considerable time so that the total recovery heat may be many times greater than the net initial heat. In the present discussion only the initial heat up to, or a little beyond, the end of the action potential is considered.

The diphasic form of the initial heat has been observed in the limb nerves of three marine crustaceans, the C fibres of the rabbit vagus and the olfactory nerves of two freshwater teleost fishes, the pike and the garfish (Abbott, Hill & Howarth 1958; Abbott, Howarth & Ritchie 1965; Abbott, Howarth & Matsumoto 1970; Howarth, Keynes & Ritchie 1968). These preparations were chosen for their physical characteristics, namely numerous small diameter fibres and, particularly in the case of the fish olfactory nerves, the comparative uniformity of the fibres. In larger diameter fibres and in myelinated fibres the events of the action potential are too rapid for there to be any reasonable expectation that available instruments could

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resolve the heat production into separate phases and, in fact, experiments made with the fin nerve of the squid and the sciatic nerve of the frog do not display any separate positive and negative components in the heat records. In the smaller and slower fibres, however, the pattern of the thermal events is so consistent and so striking that it seems it should be possible to identify the very processes which are the source of the heat changes. There is no precise test by which the source of the heat can be determined and as yet no final answer can be offered. The discussion of this problem centres on three kinds of experimental information. The first objective has been to define the time-course of the heat changes as accurately as possible in relation to the action potential. Next an attempt has been made to compare the observed heat changes with those expected by calculation on the basis of several hypotheses involving known contemporary physical events in the nerve membrane. Thirdly, a possible heat source may be tested to some degree by observing the effect of changed experimental conditions which might be expected to influence one or both of the phases of heat production.

The time course of the initial heat

The crustacean limb nerves proved to be unsuitable for any very accurate determination of the time course of heat production because of the very complex nature of the compound action potential caused by the wide variation of diameter among the fibre population. This precluded the use of any analytical procedure to determine the time course of the heat production as it would appear in a single fibre but an attempt was made by Abbott *et al.* (1958) to obtain that information by a synthetic procedure which consisted essentially of ascribing a hypothetical form to the heat production at a point in a single fibre and computing from that the form of the observed heat from a knowledge of the distribution of fibre size and conduction velocity. This was compared with the experimentally obtained heat production and the procedure repeated using various assumed forms for the original unit heat production. Although no great precision can be claimed for the method, the result is still significant for it was clear that to obtain a good fit, the positive phase of heat production had to be very brief, a feature which has been confirmed in subsequent studies. In an experiment at 0 °C the best fit was obtained by assuming that the positive phase of heat production was complete in 20 ms and the negative phase was largely complete in 100 ms but still discernible at 140 ms. This should be compared with the action potential of fibres of diameter in the range 2–5 μm which are those making the greatest contribution to the heat in the crab limb nerve, but unfortunately no suitable records are available for this.

A much more comprehensive study of the time course of the heat production has been made with the C fibres of the rabbit vagus. Here the fibres are less diverse in diameter making it possible to use an analytical procedure to study the timing. In the study by Howarth *et al.* (1967) three variations of the analytical method were employed to obtain the time of onset and duration of the positive and negative heats. At 5 °C the duration of the positive heat was found to be 73 ms and that of the negative phase 206 ms. These figures should not be compared with the considerably shorter times given above for the crab nerve which were an attempt to define the time course of the heat at a single point in the nerve. In the case of the rabbit nerve the times refer to the heat production as observed by the whole length of the thermopile on which the nerves were mounted and a comparison with the action potential was made by constructing the form of the action potential as it would be recorded by an imaginary electrode of the same length. For this purpose the unit compound action potential was recorded separately

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using a sucrose gap technique, the conduction distance being varied so as to cover the distance traversed by the action potential over the thermopile. These records were then summed to give the deduced action potential for comparison with the heat. The predicted durations of the positive and negative phases of the heat were 80 and 170 ms respectively, in good agreement with the observed values given above. The agreement was also good for the time of onset of the two phases and for the effect of varying the temperature and conduction distance. It may thus be concluded that the two phases of the initial heat coincide with the rising and falling places of the action potential. This view is strengthened by a number of experiments in which the composition of the Locke solution was changed or drugs applied which were known to affect the form of the electrical response. In almost all cases the effect on the heat production was that expected on the above view.

The time course of the heat production is still more clearly seen in the case of the olfactory nerve of the pike. Here the great uniformity of fibre diameter makes it feasible to describe the heat production at a point in the nerve, this time using an analytical procedure instead of the much less satisfactory synthetic method used for the crab nerve. At 0 °C the positive heat occupies about 60 ms and only 30 ms at 10 °C. At present there is no satisfactory way of comparing the heat with the electrical action potential in the pike nerve because of the difficulty in obtaining faithful records of the compound action potential in such exceedingly small fibres. Probably the best comparison at the moment is with birefrigence change or optical spike observed during the action potential (von Muralt 1974). The rising phase of the optical spike occupies about 35 ms in the pike nerve at 10 °C again in very good agreement with the rising phase of the heat production.

The magnitude of the heat production

The heat quantities have been conventionally expressed in terms of cals/g of wet nerve. Since it is now virtually certain that all the heat is generated at the axon surface this measure makes a comparison of different nerves rather complicated because of the varying and uncertain surface to volume ratio. The magnitude of the heat change is obtained from the experimental records after they have been analysed to eliminate instrumental lag but in many cases they suffer further distortion due to an overlap effect caused by the positive and negative phases of the fibres of different diameter affecting the thermopile at the same time and, therefore, partially cancelling out. This can only be allowed for approximately by estimating the contribution of the different fibre size groups to the total heat and calculating the extent of their mutual interference from the respective conduction velocities. Thus in the crab nerve the mean observed value of the positive heat at 0 °C was 37 μJ/g and that of the negative heat, 28.5 μJ/g. The estimated factor due to the overlap effect was 1.6 making the true value of the positive heat 58.5 μJ/g and that of the negative heat 50 μJ/g. The difference, or net heat, is, of course, not affected by any overlap effect. In the rabbit nerve the observed quantities were about the same as in the crab nerve but the overlap factor was 3.4 making the positive heat at 5 °C, 103 μJ/g and the negative heat 93 μJ/g. In the experiments with the pike nerve a short thermopile was used in order to minimize the overlap effect. This, together with the very small and uniform fibre diameter of the pike olfactory nerve was expected to lead to a substantial increase in the observed heat production but, because the limited number of experiments so far made with this preparation were intended to explore a range of conditions, there are only a few measurements available under any given condition. Nevertheless, the

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expectation is clearly fulfilled and 11 experiments made at 0 °C gave a mean observed positive heat of 184.8 μJ/g which with a 3× overlap factor corresponds to a true value of about 550 μJ/g.

The source of the heat changes

The above summary of the main facts as presently known of the thermal events associated with the action potential is perhaps sufficient to tempt some speculation about the source of the heat changes but falls short of providing a complete picture. Some important pieces of information are missing entirely and most of the quantitative data are approximate and liable to fluctuation between different experiments. What then are the possible sources of heat among the known physico-chemical events of the action potential?

An obvious candidate is the heat associated with the transfer of ions. Since the ionic exchange in the end provides the energy which drives the action potential, it is to be expected that heat changes would accompany the ion movements. However, it is difficult to see how any of the known ion movements could lead to substantial heat absorption as seen in the falling phase of the action potential, so it is most reasonable to compare the heat derived from ionic exchange with the net residual heat. In neither of the two cases where the quantities are well established is there a satisfactory fit between observed net heat and calculated heat of ionic interchange. In the crab limb nerve at 0 °C the calculated heat is three times greater than the observed net heat of 8.5 μJ/g and in the rabbit vagus which has almost the same net heat at 5 °C the calculated heat of interchange of sodium and potassium ions can account for only an insignificant fraction (about 2 %) of the net heat. Since the net heat is seen as a small difference between the two large positive and negative phases it is not unlikely that it contains some irreversible hysteresis-like element which may vary considerably with the conditions of measurement. In pike nerve at 0 °C the net heat is negative (about −20 μJ/g).

The timing of the heat production occurring with the rising and falling phases of the action potential is suggestive of a process closely linked with the polarization of the membrane and there are other indications that the heat production may be a voltage dependent process. Thus, when the rabbit vagus nerve was treated with Locke solutions of different ionic compositions, changes in the positive and negative phases of the heat production were found to follow changes in the action potential. Since the latter can be attributed to largely passive physical factors such as changes in equilibrium potential, ionic mobility and electrolyte impedance, it may be inferred that the heat production also reflects as essentially passive process rather than an active response of the membrane itself, associated with the permeability change.

A theory which accounts nicely for all the known features of the initial heat except for a precise quantitative fit is known as the 'condenser theory' in which the positive heat is attributed to the energy released by the discharge, during the rising phase of the action pontential, of the membrane capacitance, the free energy being dissipated through the action currents as joule heating. The negative heat then ensues as the capacitance is recharged at the expense of the heat of the system, charged particles being retarded in the vicinity of the membrane. In quantitative terms the fit is encouraging but not really adequate. In the crab nerve the calculated energy stored on the membrane capacitance is 18.5 μJ/g against the measured positive heat of 58.5 or 50 μJ/g if the net heat is acknowledged to arise from some separate course. In the rabbit vagus the maximum calculated energy in the membrane capacitance is 48 μJ/g and the measured positive heat is 103 μJ/g. In both cases the 'condenser theory'

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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 Götingen-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

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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

$$\Delta G = \Delta H - T\Delta S, \tag{1}$$

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),

$$\Delta G_{A\rightarrow B} + \Delta G_{B\rightarrow A} = 0. \tag{2}$$

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

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

$$\Delta G_{A\rightarrow B} = \Delta G^{\mathrm{rev}}_{A\rightarrow B} + \Delta G^{\mathrm{irr}}_{A\rightarrow B},$$

$$\Delta G_{B\rightarrow A} = \Delta G^{\mathrm{rev}}_{B\rightarrow A} + \Delta G^{\mathrm{irr}}_{B\rightarrow A}.$$

By definition $\Delta G^{\mathrm{irr}} = -T\Delta S^{\mathrm{irr}} \leqslant 0$, 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

$$Q_{\mathrm{rel}} = \Delta H^{\mathrm{rev}}_{A\rightarrow B} + \Delta G^{\mathrm{irr}}_{A\rightarrow B} \quad \text{(negative sign)},$$

$$Q_{\mathrm{abs}} = \Delta H^{\mathrm{rev}}_{B\rightarrow A} + \Delta G^{\mathrm{irr}}_{B\rightarrow A} \quad \text{(positive sign)}.$$

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

$$\Delta Q = Q_{\mathrm{rel}} + Q_{\mathrm{abs}} = (\Delta G^{\mathrm{irr}}_{A\rightarrow B} + \Delta G^{\mathrm{irr}}_{B\rightarrow A}) = -T\Delta S^{\mathrm{irr}} \leqslant 0.$$

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

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

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

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

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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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I would like to point out that the apparent discrepancy alluded to by Mr Howarth can be fully accounted for by electrostriction effects. The heat given off or absorbed by a dielectric is equal to the total change in entropy of the dielectric when the field is changed, times the temperature. For a plane disk of dielectric with the field E perpendicular to it, the heat obtained Q is given by Landau & Lifshitz (1960):

$$Q = \frac{VE^2}{8\pi}\left[\frac{\epsilon-1}{\epsilon}\frac{T}{V}\left(\frac{\partial V}{\partial T}\right)_P + \frac{T}{\epsilon^2}\left(\frac{\partial \epsilon}{\partial T}\right)_P\right] = \tfrac{1}{2}C\phi^2 K,$$

where

$$K = (\epsilon-1)\frac{T}{V}\left(\frac{\partial V}{\partial T}\right)_P + \frac{T}{\epsilon}\left(\frac{\partial \epsilon}{\partial T}\right)_P,$$

V is the volume, T the temperature, P the pressure in the dielectric, with dielectric constant ϵ, and ϕ the potential across the dielectric and C its capacitance. To calculate K, we need the following relations

$$\frac{T}{C}\left(\frac{\partial C}{\partial T}\right)_P = \frac{T}{\epsilon}\left(\frac{\partial \epsilon}{\partial T}\right)_P + \frac{T}{A}\left(\frac{\partial A}{\partial T}\right)_P - \frac{T}{l}\left(\frac{\partial l}{\partial T}\right)_P$$

and

$$\frac{T}{V}\left(\frac{\partial V}{\partial T}\right)_P = \frac{T}{A}\left(\frac{\partial A}{\partial T}\right)_P + \frac{T}{l}\left(\frac{\partial l}{\partial T}\right)_P,$$

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where A and l are the area and thickness respectively. Taking values of

$$\frac{T}{C}\left(\frac{\partial C}{\partial T}\right) = 0.45$$

for glycerol mono-oleate + n-decane (Haydon) quoted by Howarth, Keynes & Ritchie (1968),

$$\frac{T}{\epsilon}\left(\frac{\partial \epsilon}{\partial T}\right) = -0.4$$

for ethyl palmitate at 20 °C quoted by Howarth *et al.* (1968) and

$$\frac{T}{V}\left(\frac{\partial V}{\partial T}\right) = 0.3\text{–}1.0$$

for dipalmitoyl lecithin spectic mesophases by dialtometry (Melchior & Morowitz 1972).

$\frac{T}{C}\left(\frac{\partial C}{\partial T}\right)_P$	$\frac{T}{\epsilon}\left(\frac{\partial \epsilon}{\partial T}\right)_P$	ϵ	$\frac{T}{A}\left(\frac{\partial A}{\partial T}\right)_P$	$\frac{T}{V}\left(\frac{\partial V}{\partial T}\right)_P$	$\frac{T}{l}\left(\frac{\partial l}{\partial T}\right)_P$	K
0.45	−0.4	5	*0.58*	0.3	*−0.28*	0.8
0.45	−0.4	5	*0.73*	0.6	*−0.13*	2.0
0.45	−0.4	5	*0.93*	1.0	*+0.07*	3.6
0.45	−0.4	*7.7*	0.32[a]	*0.43*	0.11[b]	2.5

The values in italics are calculated from the others. *a* and *b* refer to X-ray values for dipalmitoyl lecithin (Melchior & Morowitz 1972).

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