# NERVE AS MODEL TEMPERATURE END ORGAN

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Transmission across the artificial synapse formed by the cut end of a mammalian nerve is greatly enhanced by cooling the nerve end locally (Granit and Skoglund, 1945). Considering that cooling has increased the electronegativity of this region relative to a region at normal temperature (Grützner, 1881; Verzar, 1911) it seemed worth while to investigate if by these means local cooling of a nerve could set up a discharge. It is well known that cold and heat can stimulate a nerve, and many of those who have been recording impulses from mammalian nerve twigs must have noticed effects on the discharge of dropping too cold or too hot Ringer solution on the preparation. But we are not aware of any recent systematic analyses of such effects nor have they ever been related to temperature potentials.

Bernhard, Granit, and Skoglund (1942) have put forth the general theory that sense organs stimulate their nerves by means of the electrotonic potential conducted from the end organ down the fibres depolarizing the latter. In addition, nerve serving as model sense organ has been studied in several contributions from this laboratory in which instantaneously and slowly rising electrical stimuli have been used (Skoglund, 1942; Granit and Skoglund, 1943; Skoglund, 1945). It is now attempted to find out whether or not stimulation of a nerve by temperature variations can be fitted into this model.

## Technique

The main stem of the sciatic nerve of decerebrate or chloralosed cats was locally cooled or warmed by a thermode and the discharge recorded from one of the roots, generally from the sensory L7. The thermode was a small, lacquered metal container with a cross-section like a shallow U forming a groove for the nerve and closed from above by a thin metal lid. The length of the canal for the nerve was 2 cm. The temperature of the thermode was regulated with running water and measured by a thermocouple placed at the bottom of the groove for the nerve and connected to a galvanometer. By pressing a button the experimenter marked on the film the moment when, during warming or cooling, the galvanometer spot passed a scale unit. This meant that every fourth degree of change was recorded.

The condenser-coupled amplifier for the massed discharge from the root was led to a loudspeaker as well as to a diode rectifier for integrating the total effect. This way of measuring irregular spike activity in a large number of fibres seems more satisfactory than trying to count the individual spikes. To begin with, the experiments were

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restricted to correlating the temperature at the thermode with the total integrated discharge but in the fully developed experiment the "temperature potential" was measured too. Silver-silver chloride electrodes were taken to the midpoint of the cooled or warmed region (the lid of the thermode having been removed) and to a point on the nerve about 5 cm. farther up. These were connected to a condenser-coupled amplifier capable of recording fairly well the initial phase of the slow temperature potential. The amplifier response to a calibration potential fell to half its full value in 10 seconds. Some controls were made with an electrometer, consisting of two push-pull coupled electrometer valves operating a moving coil galvanometer. With this apparatus it became possible to see how well the temperature potential was maintained. In the standard experiments, however, the temperature potential was recorded by the condenser-coupled amplifier operating one beam of a double-ray cathode ray oscillograph whereas the other beam recorded the integrated massed discharge from the root.
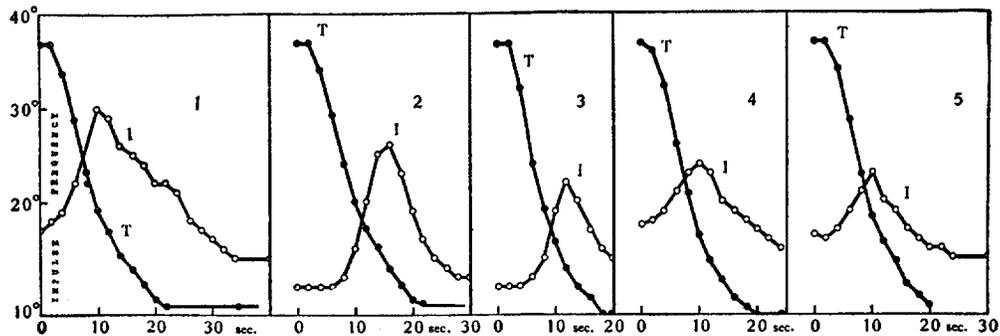


FIG. 1. Five successive observations (1–5) on the effect of local cooling of cat's sciatic upon discharge, I, recorded from root, as described in text. Ordinates: temperature of thermode (Curve T) and integrated relative frequence of nerve impulses (Curve I). Abscissae: time in seconds.

The fully developed technique utilizing the double-ray oscillograph as described above, became necessary in order to correlate the temperature potential with the impulse discharge. But several simpler problems were taken up before this stage was reached and for these cathode ray and photographic recording were not employed. One experimenter read off the temperature on the galvanometer connected to the thermocouple, the other one the values on a galvanometer connected to the diode rectifier integrating the total impulse frequency. A metronome was used for synchronizing the readings and marking time.

RESULTS

*The General Effect of Local Cooling and Warming.*—The experiment shown in Fig. 1 was carried out with a decerebrate cat. The thermode was on the intact sciatic at the knee, the hamstring nerve severed, and the motor and sensory roots L7 cut and isolated.

Chart 1 of Fig. 1 illustrates the stimulating effect of a rapid fall of tempera-

ture. The discharge has been recorded from the sensory L7. In Chart 2 the recording electrodes have been shifted to the motor root. There is less spontaneous activity on the motor side—which, of course, is typical—as shown by the lower initial level of the impulse integrator. The excitatory effect of local cooling passes over in a shorter time. In Chart 3 the sciatic stem has been tied $1\frac{1}{2}$ cm. from the lower edge of the thermode and the experiment repeated. In Chart 4 the same experiment has been carried out with the electrodes shifted to the sensory L7. Finally, in the experiment of Chart 5, the nerve has been cut at the lower edge of the thermode. This led to a great increase of spontaneous activity lasting for a few minutes. When this effect had disappeared the experiment of Chart 5 was carried out in the same manner as before. The gradual diminution of the effect of cooling from 1 to 5 is typical and need not be ascribed to the severance of the nerve. The artificial end organ always works best in the beginning of an experiment. Repetition diminishes the discharge. The five experiments were carried out in succession and the nerve at the thermode warmed up between each of them.

It is clear that local cooling of a nerve is an effective stimulus capable of causing a massive but transitory discharge, provided that the nerve is in good condition and the animal not too deeply anesthetized. Generally about 2 hours were allowed for disappearance of the immediate effects of the initial anesthesia. When chloralose was given the dose was kept below 6 cc./kg. of a 1 per cent solution.

It is seen in Fig. 1 that the excitatory effect of local cooling is given both by intact nerve and cut end. When the thermode was at the cut end the spontaneous activity from this region was a good index of the general state of the autorhythmic mechanism responsible for the discharge itself. For this reason severed nerves were later used in nearly all experiments. All experiments agreed in showing that the final effect of cooling the nerve locally to some 8–12° C. consisted in practically complete cessation of impulse generation within the cooled region.

It is therefore concluded that the excitation caused by local cooling, is counteracted by an opposite process of immobilization of the discharging mechanism of a nerve. The completeness of this immobilization is not very well shown by Fig. 1 because the cut hamstring nerve continues to discharge so that the integrator never falls down to zero. But it is well brought out by Fig. 5 showing the integrator connected to the cathode ray oscillograph and was regularly confirmed by looking at the massed discharge on the screen of the cathode ray and by listening to it in the loudspeaker. The baseline, broadened by spontaneous and induced activity from the cut end, shrank to a thin line after the transient excitatory effect of cooling and remained so as long as the thermode was kept cold.

If the cooled nerve was warmed through the thermode at the same rate at which it had been cooled and thus brought back to its original temperature

between 36 and 40°, the spontaneous firing from the cut end was resumed. But this effect was late in starting. A latency of some 30 to 120 seconds preceded recovery of the autorhythmic mechanism to be compared with the latent period of a few seconds, that preceded the excitatory effect of cooling.

There is thus, as one would expect, a general effect of temperature on the autorhythmic mechanism of discharge in the sense that cold suppresses and warmth enhances the spontaneous activity set up by the cut end. This general
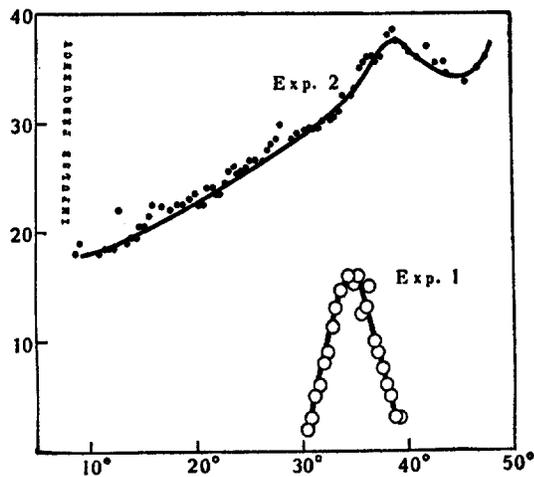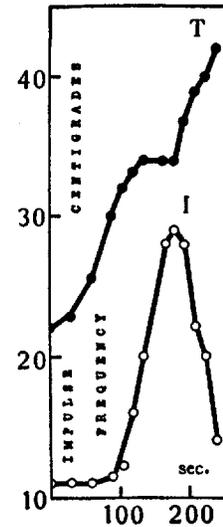


FIG. 2

FIG. 3

FIG. 2. Integrated frequency of discharge (ordinates) from cut end of sciatic during slow warming of thermode (abscissae in degrees Centigrade) at the nerve end. Two different animals.

FIG. 3. Depression by warming. Ordinates: temperature (Curve T) in degrees Centigrade and integrated relative frequency of nerve impulses (Curve I). Abscissae: time in seconds.

effect can be isolated and studied alone if the temperature changes are brought on very slowly.

It could easily be shown that stimulation by cold was a function of the rate of change of temperature because if the thermode was cooled very slowly the excitatory effect was negligible, and the impulse activity gradually subsided. Such experiments were used in order to find out whether an optimum temperature could be demonstrated. Fig. 2 shows two experiments in which there were optima in the sense that a slow *increase* of temperature, beyond 40° in the one case, and beyond 36° in the other, again led to a diminution of the spontaneous discharge. The former experiment also demonstrates that a further increase

of temperature above normal re-activated the nerve. This was, in fact, the most regular effect of warming the nerve beyond the maximum which corresponds to the upper limit of body temperature. This re-excitation at high temperatures, which for the moment we shall neglect, was not, as a rule, noticeable below 44° but may, of course, already below that temperature have contributed to the blotting out of the optimum.

The main point to be raised here is that an optimum, when present, shows that local warming of the cut end not only excites but also may inhibit the spontaneous discharge though the inhibitory effect is difficult to demonstrate because it is always pitted against the general favourable effect of raising the temperature. Fig. 3, however, shows one of the cases in which the spontaneous discharge was suppressed by a moderate fast rise of temperature.
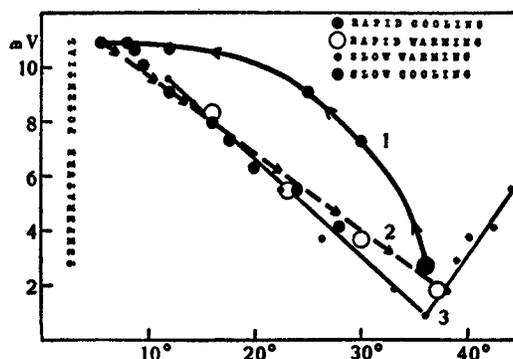


FIG. 4. Temperature potentials, recorded as explained in text.

The general conclusions reached in this section are thus that, apart from the expected favourable effect of warmth and unfavourable effect of cold on the discharge from the cut end, cold causes a strong transitory excitation and warmth a less definite but sometimes demonstrable inhibition. All these observations refer to temperatures at or below the normal range.

*The Temperature Potentials.*—It is known that a cooled region of a nerve becomes negative relative to some point at normal temperature (Grützner, 1881; Verzar, 1911). Since no D.C. amplifier was available for use with the oscillograph, two electrometer valves were set up in push-pull coupling in order to find out how large these potentials were and how well they were maintained in our experiments. The temperature potentials were recorded by a sensitive moving coil galvanometer on a scale on which 1 mm. corresponded to 0.91 mv. Only two animals were used with this technique. Most experiments on temperature potentials were carried out with the condenser-coupled amplifier connected to the oscillograph (see Technique).

The result of the experiment giving the larger temperature responses is shown in Fig. 4. The points, marked 1, are the first set of observations. The ther-

mode temperature was originally 36°.   In 15 seconds the temperature was then brought down to 8° and this made the nerve end more negative by 8.2 mv. Further cooling to 5.6° did not increase the negativity which was maintained for 1 minute.   The temperature at the thermode was next (Curve 2) increased to 36° in 15 seconds.   The potential returned to its original value along the curve marked 2.   This final value was also maintained.   Then followed slow cooling during 9 minutes, the points falling along Curve 3 together with those marking the effect of the final slow warming of the nerve during much the same length of time.   The temperature was ultimately increased to 44° and it is seen that in this region of supernormal temperature the nerve again responded by increased negativity of the region in the thermode relative to normal nerve.

Thus, from low temperature to the normal range the nerve works like a kind of thermocouple the "cold junction" becoming electronegative relative to the "warm junction."   Above the normal range its properties are reversed.

Seeing that the nerve discharges not only when cooled but also when heated above the normal range and that in both these cases the discharging region becomes electronegative relative to a portion at normal temperature it was held to be of great interest to record the temperature potential and the discharge simultaneously, and with sufficiently fast instruments, in order to ascertain whether the electronegativity precedes the discharge or not.   This was carried out by means of a second condenser-coupled amplifier, taken to the second beam of the double cathode ray oscillograph, as described in the section on Technique.

In the record of Fig. 5 the cold potential and the integrated impulses discharged by the cooled end are photographed together.   This shows that the cold potential began to rise *before* the rise of the discharge set in.   The excitatory effect of cold on the discharge was found to follow between, on an average, 2.2 to 3.4 seconds after the first sign of the rise of a cold potential.   The shortest interval noted was 1.4 seconds but this was in an experiment with extremely high amplification for the integrator so that the baseline was rather irregular owing to the spontaneous activity from the cut end.   This is also seen to cause oscillations of baseline before cooling, in the experiment of Fig. 5.   The unusually short latency of 1.4 seconds in one experiment was probably due to a spontaneous volley just preceding the effect of cold.

The simultaneous records thus showed that without exception the transitory discharge, elicited by local cooling of the nerve began when a certain amount of potential difference had been set up between the cooled point and normal nerve, just as the optic nerve begins to discharge in response to a stationary potential across the sense cells.   The temperature potentials recorded by this technique were smaller than those obtained in the electrometric experiments. When corrected for the exponential character of the amplifier response (see Kohlrausch, 1930) the temperature responses were around 0.1 to 0.15 mv. per
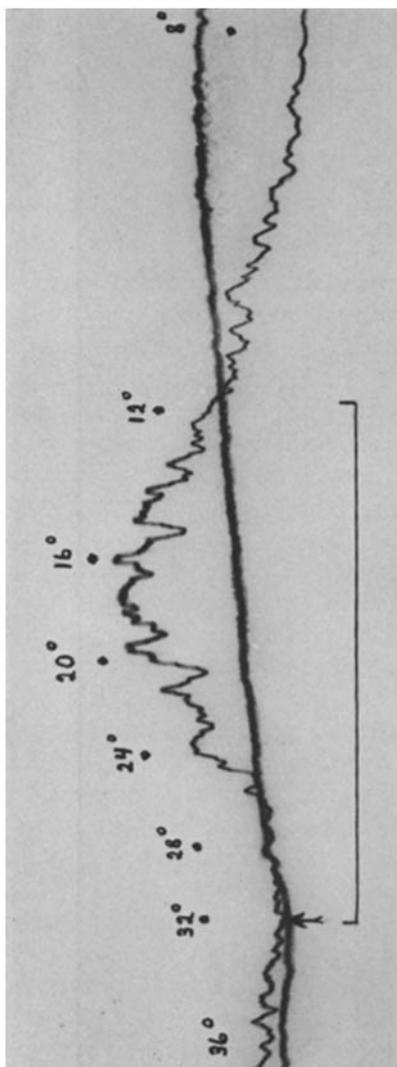
FIG. 5. Simultaneous oscillographic records of cold potential rising at arrow and integrated impulse frequency during cooling of thermode at cut end. Line below marks 5 seconds. (Note that integrator falls below original level of spontaneous activity at 8°.)

degree as against up to 0.3 mv. per degree with the electrometer valves.    Generally the potential difference was maintained as long as the low temperature was maintained.

On repetition of such experiments several times in succession it was found that the autorhythmic mechanism of the nerve gradually became less sensitive to stimulation by cold.    The temperature potential also diminished somewhat but it often happened that the nerve almost had lost its capacity to respond to cooling by impulse activity at a time when the cold potentials still were almost normal.

## DISCUSSION

When speaking of nerve as model temperature end organ this is not done in order to call attention to the general unfavourable effect of cold on the spontaneous activity and to the restoration of this activity by warming up the nerve to normal temperature.    This finding is merely regarded as an expression of general temperature effects of which no more need be said in this connection. The nerve serves as a model cold end organ in the sense that rapid local cooling sets up a discharge of impulses which is preceded by a potential change of such a character that a discharge must be expected from the cooled region.    It is assumed that this potential difference, making the cooled end negative to the rest of the nerve, generates the discharge and that the maintained state of electronegativity would continue to do so, merely hampered by accommodation, were it not for the fact that cold has a general unfavourable effect on the autorhythmic mechanism.    Hence the transitory character of the discharge.

Warming the "artificial end organ" removes this generator potential.    The circumstance that warmth has a general favourable effect on the discharge counteracts the diminution of the impulse activity that otherwise would be a consequence of diminished electronegativity of the "end organ."    Under favourable conditions, however, this opposite effect of warmth relative to cold can be distinguished.    Assume now that there would be a certain amount of spatial separation between an "end organ" and the discharging region of its nerve so that the former could be cooled without paralyzing the latter.    The resulting structure would be something analogous to the fish *Lorenzinian ampullae* which were found by Sand (1938) to respond to cooling by discharging and to warming by cessation of impulse activity.    Their mechanism of excitation may well be of the kind described in this paper.

The applicability of the model is perhaps more striking with respect to cooling.    The mechanism is quite sensitive.    A quick fall of 1° may cause a discharge in a good preparation.    The generation of impulses in response to heat is provided for by the model in the impulse activity which is a consequence of warming the "end organ" above the normal range.    Its mechanism is apparently similar to the generation of impulses by cold.    The "end organ" again

becomes negative relative to normal nerve.   We need but imagine a certain amount of development and specialization of the temperature end organs, based on the general principles described in this paper, to possess a basic theory for how cold and heat excite their receptors to set up impulse activity in the nerve fibres.

## SUMMARY

Rapid local cooling of mammalian nerve sets up a discharge which is preceded by a local temperature potential, the cooled region being electronegative relative to a normal portion of the nerve.

Heating the nerve locally above its normal temperature similarly makes the heated region electronegative relative to a region at normal temperature, and again a discharge is set up from the heated region.

These local temperature potentials, set up by the nerve itself, are held to serve as "generator potentials" and the mechanism found is regarded as the prototype for temperature end organs.

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