

## ADAPTATION OF CUTANEOUS TACTILE RECEPTORS. II

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### I

A method of recording action potentials from individual nerve fibers supplying single receptors in the skin of the frog has been described (Adrian, Cattell, and Hoagland, 1931; Hoagland, 1932). Leads are placed on a dorsal cutaneous nerve which has been cut near its entrance to the skin, and antidromic impulses are recorded. These impulses are set up by stimulating a single receptor supplied by an axon which branches in the dorsal root ganglion and sends a fiber out along the dorsal cutaneous nerve under investigation. Thus the impulses travel from the receptor to the ganglion and then out again to where they are recorded without having entered the central nervous system or passed a synapse. The action potentials are amplified and recorded with a Matthews oscillograph used in conjunction with a camera, a standing wave screen, and a loud speaker. Stimulation of the tactile receptor preparation at any desired frequency, duration, or intensity may be secured by applying to the skin surface a jet of compressed air interrupted by a toothed disc fitted to a flexible shaft and revolved by a motor.

"Adaptation" to a constant pressure was found to be very rapid—only one or two impulses being set up. With repeated air blasts of short duration ( $5\sigma$ ) only a single impulse is set up for each puff of air. If the frequency is sufficiently great the end-organ soon fails to follow every stimulus, more and more impulses being dropped out until the response ceases entirely. The failure depends not only upon the frequency of stimulation but upon the duration of the stimulus and the interval between stimuli. The time of complete failure of response may be regulated in terms of these variables from a few seconds to more than an hour (Cattell and Hoagland, 1931).

Studies have been made of the rate of adaptation of tactile receptors as a function of the properties of a series of discs used to interrupt the air jet (Hoagland, 1932-33*a*). Empirical equations were determined for the failure of response, and equations relating the velocity constants of these equations to the ratio of  $S/R = \frac{\text{Stimulating time}}{\text{Time between stimuli}}$  as determined by the relative area occupied by the notches and the intervening solid material of the discs.

## II

A general hypothesis concerning a possible mechanism of adaptation, that is, of failure of nerve impulses set up in response to repeated pressure stimulations of single tactile receptors, is here presented and discussed in the light of a group of experimentally ascertained facts concerning the phenomenon.

Encapsulated receptors in frog's skin are histologically rare. The receptors ( $\pm 200$  per  $\text{cm}^2$ ) may be regarded as free nerve endings branching among cells of the epithelium (*cf.* Adrian, Cattell, and Hoagland, 1931). They may be viewed as stimulated directly by mechanical movement of the skin which sets up tension and stretches the filamentous endings. The stimulus may thus be regarded as acting in a way similar to that of pressure on an excised nerve trunk—a constant applied pressure, in general, sets up impulses only momentarily during its application and again occasionally on its removal, the nerve apparently “adapting” itself to the constant pressure in a manner similar to the adaptation of excitable tissues to the flow of a constant current. Repetitive applications of pressure may be regarded as repeatedly stretching the nerve and stimulating it, perhaps by physical alteration of its polarized membranes. As in the case of repetitive, non-injurious stimulation of excised nerve we might expect impulses to be set up in response to each stimulation, provided the intervals between stimuli do not exceed the refractory period of the nerve. Such repetitive activity of excised nerve has been found to be maintained over long periods of time.

The failure of response of the cutaneous endings to the repeated stimulations of the air jet has been referred to above as sensory adaptation. The receptive nerve fiber is surrounded by epithelial

cells which are distorted by the mechanical stimulus and it is not unreasonable to suppose that substances may be released from the cells surrounding the fiber as a result of their distortion. Such substances accumulating about the fiber may progressively lower its excitability, ultimately silencing it by increasing its threshold to stimulation.

Adrian, Cattell, and Hoagland (1931) reported that if the surface layers of frog's skin were scraped away the tactile responses (nerve impulses) ceased for a time but eventually returned. Feng (1933) confirmed this and extended the observations, showing that the failure was due to the release of potassium from broken epithelial cells, which temporarily reduced the excitabilities of the endings. Feng found that the temporary abolition of responses occurs not only in the region scraped, but also in adjacent unscraped regions. Irrigation with Ringer's solution caused the responsiveness to return. Samples of scraped and unscraped frog's skin were applied to the underside of the skin-nerve preparation. Inhibition of response occurred only when the preparation was in contact with scraped skin. The inhibitory effect was found not to be peculiar to damaged skin alone. Crushed frog tissues in general were found to inhibit the tactile nerve impulses. The effect was shown not to be due to pH or to osmotic pressure changes.

Ringer's solution with about ten times the normal potassium content was also found to inhibit responses, as did solutions made up of ashed tissue extracts. Potassium assays were made of the inhibiting tissue extracts which were found to inhibit to about the same degree as solutions containing equal amounts of potassium.

This work is suggestive in connection with the quantitative analysis of the spread of effects of operational injury along the lateral-line receptors of fishes (Hoagland, 1932-33*b*). A depressing action on spontaneously discharged nerve impulses from the neuromasts was found for a distance of  $\pm 2$  cm. from the region of operation, the inhibitory effect decreasing with the distance from the incision. The high mobility of potassium ions is consistent with the notion of its production of such injury effects.

Blinks (1933) has reported the inhibition of recovery in the presence of potassium after the passage of action currents in cells of *Nitella* and

*Chara*. He suggests that the effect is due to a lowering of acidity within the cells by the entrance of potassium in the form of a base. (For a review of the relation of potassium to bioelectric currents in plant cells *cf.* also Osterhout, 1931.)

The following facts appear to be consistent with the hypothesis that adaptation of tactile receptors may be due to the liberation of potassium from surrounding epithelial cells when pressed upon, reducing the excitabilities of the nerve endings to direct mechanical stimulation.

### III

(a) Experiments involving brief durations of the air puff stimulus show that the receptor can follow frequencies of stimulation of the order of 350 per second for a short time ( $\pm 0.5$  second) at room temperature. The brief intervals between stimuli at these high frequencies may force the nerve to conduct in its relative refractory period, giving axon potentials which may be reduced 50 per cent below normal (Cattell and Hoagland, 1931). The brief time relations involved imply that the stimulus effects the fiber directly, without the mediation of chemical mechanisms.

(b) Adaptation to a jet of air at constant pressure stimulating at 140 impulses per second was measured with eleven single-fiber preparations. The time of complete adaptation was recorded with a stop-watch by observing the failure of impulses on a viewing screen. After complete failure of impulses a jet of Ringer's solution was passed from a pipet across the *under* side of the skin through an incision a few millimeters from the ending. The solution drained away through a second skin incision below the ending. The washing in all but two cases effected a rapid recovery of the ending—impulses being produced from the previously adapted receptor, not only during the washing, but for about half the normal adaptation time after cessation of the current of Ringer's solution.

It was thought that the apparent recovery might have been due to slight elevation of the skin towards the stimulating nozzle by the entering solution, thus rendering the stimulus more effective. Accordingly the skin was lifted slightly by the tip of the pipet and also by blowing air through the pipet against the under side of the skin. In

a few cases slight augmentation of the response seemed to result but to no such degree as was observed when the skin was washed with the current of Ringer's. In six experiments isotonic KCl was used to

TABLE I  
Stimulation frequency = 140/second

Time required for complete failure of impulses, with different durations of recovery between determinations			
60 sec. recovery period	30 sec. recovery period	15 sec. recovery period	Approximately 3 sec. recovery period
<i>sec.</i>	<i>sec.</i>	<i>sec.</i>	<i>sec.</i>
15.2	15.0	8.2	2.2
15.0	14.6	7.2	1.8
14.8	15.4	7.6	3.0
15.6	14.8	8.4	1.2
15.4	15.2	8.8	2.0
Means . . . . .15.2	15.0	8.0	2.0

Immediately after complete adaptation, with the intermittent stimulus continuing, the skin was washed with Ringer's solution for a period lasting  $8 \pm 2$  sec.

Time from start of washing to second complete adaptation	
<i>sec.</i>	
20.2	
25.8	
18.0	
26.0	
23.8	
Mean . . . . .22.8	
After washing with isotonic KCl (30 sec. recovery period), adaptation time:	
<i>sec.</i>	
6.0	
2.0	
0.0	

Repeated washing with Ringer's solution produces complete recovery.

wash the under side of the skin. This qualitatively caused a hastening of adaptation. Washing with Ringer's solution after the failure due to KCl hastened the recovery. Table I shows the results of one experiment.

(c) The speed of adaptation is increased with increase in the ratio of  $\frac{\text{Stimulating time}}{\text{Time of rest between stimuli}} = S/R$  as determined with a series of notched discs used to interrupt the air jet (Hoagland, 1932-33*a*). In some preparations the velocity constant of the process of adaptation was found to be directly proportional to  $S/R$ ; in others it was proportional to its logarithm.

This is consistent with the notion that potassium released from surrounding cells reduces the excitability of the nerve fiber—the greater the value of  $S/R$  the more rapidly potassium would be released and the faster would be the sensory adaptation. The excitability of nerve depends on the ratio of potassium inside the fiber ( $K_i$ ) to potassium outside ( $K_o$ ), where  $\frac{K_i}{K_o}$  is normally about 10 (*cf.* Hill, 1932). Potassium released from surrounding epithelial cells would tend to decrease this ratio by raising  $K_o$ , thus reducing the excitability of the nerve fiber. For a review of the relation of the excitability of muscle to its potassium content *cf.* Needham (1932, chapter 7).

In nine out of fifteen preparations studied the frequency of response of the ending to the air puff stimulus was found to decline logarithmically with time. This is consistent with the notion that diffusion of potassium may be the determining factor in producing adaptation. In six out of fifteen cases the frequency declined hyperbolically and at a more rapid rate than in the other experiments. This digression from the logarithmic decline may have resulted from the fact that in some preparations the recovery mechanism maintaining  $\frac{K_i}{K_o}$  may have been retarded, thus facilitating the accumulating potassium and producing adaptation.

(*d*) A series of preliminary experiments on adaptation as a function of temperature has been carried out by the writer in the laboratory of W. J. Crozier at Harvard. A satisfactory quantitative analysis of these results is not yet complete. Qualitatively, however, adaptation is found to be faster the lower the temperature. This may be due in part to the fact that at lower temperatures the skin appears to be less flexible, as judged by its movement in response to the stimulus, thus rendering the pressure less effective and reducing the stimulus to

nearer the threshold value for the receptor. Any increase of potassium ions from epithelial cells in the vicinity of the fiber would tend to be more effective in reducing the excitability of the nerve owing to reduction of the effective stimulus, despite the fact that presumably less potassium would be released at lower temperatures. It is also probable that at low temperatures chemical recovery processes of the nerve maintaining the ratio  $\frac{K_i}{K_o}$  would be reduced, resulting in an increased rate of failure during repeated excitations.

Table II shows that the frequency of the functional occurrence of antidromic tactile endings increases with temperature. This may be the result of greater pliability of the skin at higher temperatures resulting in more vigorous movements of the stimulated skin and hence

TABLE II

Mean experimental temperature. ± 0.3° approximately	No. of frogs	Total No. antidromic endings	Antidromic endings per frog
°C.			
7.2	15	24	1.6
11.1	10	22	2.2
15.0	11	28	2.5
18.6	4	12	3.0
24.7	6	24	4.0

more effective stimulation. Thus receptors of high thresholds of activation may be stimulated more effectively at higher temperatures. The increase in the number of observed responsive antidromic endings with temperature may also be accounted for in terms of facilitation of chemical factors involved in regulating thresholds of excitability of the nerve endings; *i.e.*, in producing augmentation of the ratio  $\frac{K_i}{K_o}$ .

Throughout the course of the experiments it has been repeatedly observed that the degree of movement of the skin makes considerable difference in the time of adaptation for the same preparation. A difference of 100 per cent in the time of complete adaptation may be obtained by merely altering the angle at which the stimulus impinges upon the skin. In quantitative studies of the single endings it has

therefore been found essential to keep the position of the nozzle with respect to the skin rigidly fixed throughout work with a particular preparation.

(e) Cattell and Hoagland (1931) found that if an uninterrupted jet of air was applied gradually for approximately 30 seconds to a single

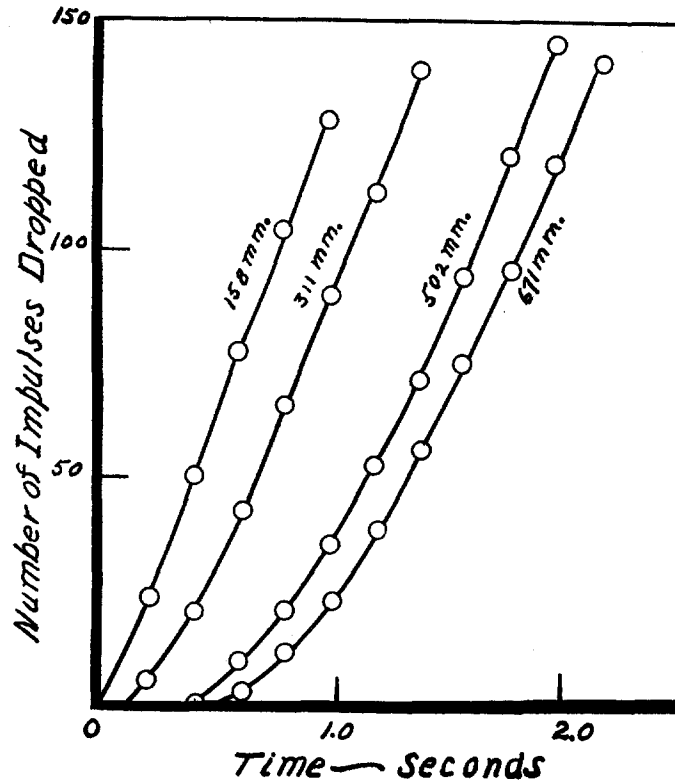


FIG. 1. Adaptation curves for a single ending at different pressures (mm. Hg). The data were obtained by counting, from photographs, the number of impulses dropped after the beginning of stimulation at zero time. The stimulation frequency was 140 per second.

receptor, setting up no nerve impulses, the receptor nevertheless became, by this treatment, adapted to a normally effective intermittent air jet applied immediately afterward.

This finding is consistent with the proposed general hypothesis—



the slowly increasing pressure is unable to excite the fiber but it may nevertheless cause leakage of potassium from the epithelial cells. Thus the ratio of  $\frac{K_i}{K_o}$  of the nerve fiber may be reduced by the increase in  $K_o$  so that a subsequent interrupted stimulus becomes ineffective.

(f) It was also reported by Cattell and Hoagland (1931) that stimulation of a part of a given skin area supplied by a single branching axon produced adaptation, not only in the stimulated area, but also to a second intermittent stimulus applied immediately after the first, to an adjacent area several millimeters distant, supplied by the same branching axon. In terms of the present hypothesis this is to be expected owing to the diffusion of potassium ions, released from epithelial cells by the stimulus, to the neighboring area (*cf.* discussion of Feng's experiments).

(g) Recent experiments indicate, in general, that adaptation of the tactile receptors is faster at lower pressures. Fig. 1 shows this relation. Lowering the pressure decreases the movement of the skin and hence the adequacy of the stimulus, so that the stimulus approaches more nearly its threshold value. Presumably less potassium will also be released from the epithelial cells, producing less effect on the excitability ratio  $\frac{K_i}{K_o}$ . However, if the adequacy of the stimulus declines rapidly with pressure, even a small increment in  $K_o$  may be sufficient to produce rapid sensory adaptation.

#### SUMMARY

Studies of axon potentials set up by pressure stimuli applied to single cutaneous receptors in frog's skin indicate that the mechanical stimulus excites the free nerve endings directly.

Adaptation to constant pressures or to intermittently applied pressures (failure of the response) may be due to the reduction of excitability of the nerve endings by potassium released under the pressure from surrounding epithelial cells.

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