

THE "INHIBITORY" EFFECT OF HIGH-FREQUENCY
STIMULATION AND THE EXCITATION
STATE OF NERVE.

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HILL and his collaborators have noted and examined in some detail the unexpected effect of high-frequency stimulation of nerve. Up to moderate values, 400–600 per sec., the response—either heat or action potential—increases with frequency as if to an asymptotic value. At higher frequencies, however, the conducted response progressively diminishes: by 50 p.c. or more at 2500 per sec. and, by extrapolation, almost to zero at 5000, or with stimuli spaced at 200 micro seconds.

In general terms, the decreased activity could be due to one or all of three types of effect, easily distinguished experimentally. (1) The fast stimulation might set up propagated activity of low intensity by some form of over-driving of the fibres. In this case, as in the classical Wedensky effect, additional stimuli applied at a slow rate at any position or phase should be entirely ineffective or even slightly augment the inhibition. (2) The fast stimulation may so alter the nerve locally under the electrodes that it becomes less irritable and conductive, some fibres perhaps being completely blocked, and all fibres able to carry fewer impulses per sec.—not unlike an anelectrotonic state. Slow stimuli applied at a point "downstream" should then be fully effective and produce a response equal to or even slightly above that of slow stimulation alone. If applied at or above the region of fast stimulation, however, adding slow stimuli would not increase, possibly slightly decrease, the response. (3) Rapid stimulation may largely fail to excite (as is the case for high-frequency sine currents) without greatly altering the ability of the nerve to conduct impulses or to be excited by lower frequencies. If this were the situation, superimposing low frequencies on high ones should lead to approximately

maximal responses, whether applied above, at or below the region of high frequency stimulation.

Experiments were performed to test these possibilities, using the action potential, recorded with calomel electrodes at a distance from all points of stimulation, as the index of conducted response. High-frequency stimuli (condenser discharges through a commutator) were applied through silver or calomel electrodes at a frequency of 2300 or more one-way or 4400 two-way discharges per sec. Low-frequency stimuli (obtained from an independent commutator-condenser set-up) were one-way discharges at 500–600 per sec. through calomel or silver electrodes. Usually a discharge time, to $1/e$, of 2×10^{-5} sec. was used. That both sets of stimuli were equivalent, except for frequency, was shown by reducing the frequency of the “fast” stimuli to that of the “slow”—when both gave the same action potentials. Escape of stimulating currents to the pick-up electrodes did not occur, except with excessive stimuli: grounding the nerve between stimulating and lead-off electrodes made no significant difference in the galvanometer deflections, whereas killing the nerve or blocking with a constant current abolished them.

RESULTS.

L (low-frequency) below H (high-frequency). In all cases the full *L* response, or slightly more, is obtained when *L* stimuli are applied downstream to *H*. Typically, when *L* is “on,” turning *H* on or off has no effect on the deflection.

Sometimes a small increased response results from $H + L$, as if a few fibres respond more to *H* than to *L*. The same sometimes occurs when *H* is lowered to the frequency of *L* (e.g. $H = 235$, $L = 235$, $H + L = 250$) and may mean only an anatomic unavailability of fibres to one or the other electrode. Results of two series of three and four runs at usual frequencies were: $H = 120$, $L = 220$, $H + L = 235$; and $H = 50$, $L = 90$, $H + L = 95$. Hill reported a similar experiment, using heat production as the measure of response [Bugnard, 1934], with a similar result.

Clearly, the diminished response to high-frequency stimulation does not depend on conducted activity of low intensity or on a special propagated “inhibition,” but rather on a failure to set up the usual nerve impulses. To what extent this failure is the result of some form of local block by *H*, and to what extent it is a failure of *H* to reach a threshold value for all fibres is indicated by applying the *L* stimuli at or above the region exposed to *H*.

L or H partly or wholly interpolat to other. In general, any such combination permits a maximal or nearly maximal response when *L* is on

whether H is on or off. It is necessary, however, to consider the separate cases and especially the current direction. With the cathode of H distal (downstream) and between the two electrodes of L , the full response is obtained. Similarly, when H and L are both applied to the same pair of electrodes (distal H electrode either cathode or alternating, and L cathode or anode distal), the maximal response is obtained, at least when the H voltage is not too high. Thus in two runs: (1) H cathode distal: $H=55$, $L=200$, $H+L=200$; (2) H alternate discharges: $H=130$, $L=165$, $H+L=165$.

The case of L interpoar to H is especially interesting, as either the cathode or anode of H (or both with alternate shocks) can be interposed between L and the region of recording. Mostly, the direction of H was immaterial and responses to L were complete or large—putting on L always gave a marked increase over H alone.

Thus the average of seven runs in two series was: (1) H cathode distal: $H=65$, $L=145$, $H+L=145$; (2) H cathode proximal: $H=25$, $L=170$, $H+L=165$; (3) H alternate: $H=90$, $L=140$, $H+L=135$. In one experiment, however, the impulses set up by L stimulation were completely blocked by the cathode of H (cathode distal) and were completely passed by the anode (cathode proximal): H cathode distal— $H=50$, $L=200$, $H+L=50$; H cathode proximal— $H=55$, $L=200$, $H+L=200$. The block occasionally produced by H is more satisfactorily considered in relation to the following series of experiments.

The prime indication of this series is that the nerve stretch acted on locally by H stimuli is still quite able to respond maximally to added L stimuli of the usual just supramaximal intensity. It seems to follow that diminished responses to high frequency stimuli are primarily due to a failure of these stimuli to excite.

L above H. The preceding experiments test, roughly, the "irritability" of the nerve stretch exposed to H ; the present ones similarly test its "conductivity." The general result is, again, that the H region does not offer a serious barrier to the passage of ordinary impulses initiated upstream. A partial or complete block was, however, not uncommonly encountered; and several experiments were directed, with only partial success, to an analysis of the factors determining its appearance. A survey of the basic results is given in Table I.

TABLE I.

Exp.	Runs averaged	H	L	$H+L$
1	4	45	70	40
2	4	155	205	195
3 (early)	6	140	205	140
3 (later)	11	130	185	185
4	1	120	295	260
5	3	135	295	280

In each case consistent results were obtained, except that *L* was completely blocked at first in exp. 3 and completely transmitted later, with no deliberate alteration of the experimental conditions. In most cases the presence or absence of a ground on the nerve between stimulating and recording electrodes made no difference. Other checks to eliminate the possibility of the *L* stimuli spreading past the *H* region and acting, directly, on the normal nerve beyond included: (1) Reducing to maximal or submaximal intensity, supramaximal *L* stimuli that were "coming through" the *H* region. There was no difference except that with very strong stimuli the total *L* response (*H* on or off) was greater by about 20 mm. on 200—almost surely a direct leak into the galvanometer circuit. (2) Moving *L* upstream, and away from the *H* region, as much as 2 cm. had no influence. (3) Applying a constant current (2 volts) at the *H* electrodes blocked conduction and abolished responses to *L*.

One important factor is the frequency with which impulses arrive at the *H* region. On varying the frequency of *L* several times from 150 to 1000, average results were: *L* at 450 per sec.: *H* = 80, *L* = 260, *H* + *L* = 220; *L* at 600 per sec.: *H* = 85, *L* = 250, *H* + *L* = 340; *L* at 1000 per sec.: *H* = 50, *L* = 195, *H* + *L* = 110. It is interesting that at 1000 per sec. the *L* stimuli begin to show the "inhibition" of high-frequency, and at the same time are largely blocked by the *H* region. The same blocking of high-frequency impulses is shown using *H* alone by changing current direction. Thus the following responses were obtained to *H*, in each set using the same electrodes (Table II).

TABLE II.

Exp.	Cathode distal	Cathode proximal	Alternate
1	35 (3)	40 (1)	35 (3)
2	130 (9)	5 (6)	150 (5)
3	75 (1)	55 (1)	140 (1)
4	120 (2)	30 (2)	—

With a single exception, the response was distinctly greater when impulses arising at a distal cathode could travel directly on than when, arising at a proximal cathode, they had to pass the anodal region. Several interpolar lengths, from 2 to over 20 mm., were used; and the proximal electrode was moved near to or far from the cut end of the nerve; with no difference.

These results speak then, for a block of high-frequency impulses at the anode of high-frequency stimuli. (The influence of alternate shocks will be considered later.) It is to be expected that the more rapid an impulse train—with consequent lowering of impulse intensity by traveling in relatively refractory periods—the more easily will block occur at a region of slightly increased threshold. This is entirely comparable to the classical Wedensky effect [see Kato, 1929; Gerard, 1930]. A progressive slowing of reactions, with rise of threshold and prolonged refractory period due to equilibration, would help account, along similar lines, for the falling-off of the *H* response on continued stimulation. (Through all the discussion, decreased response is to be interpreted as due to fewer active fibres, or fewer or feebler impulses. The latter could only occur at frequencies falling within the refractory period, which is, however, prolonged. Field and Brücke, 1926; Gerard and Forbes, 1928;

Bugnard and Hill, 1935. The dropping out of fibres in statistical fashion is probably a large factor.)

Returning to the factors that determine whether or not *L* impulses pass the *H* region, the direction of *H* may play a minor rôle. In one experiment, *L* came through almost entirely when *H* was cathode distal, and 70 p.c. when cathode was proximal; so that passing cathode-anode seems somewhat more difficult than the reverse order. But of special interest is the influence of magnitude of the *H* stimuli. The stimulating, "inhibiting" and blocking effects of *H* do not in fact run parallel as *H* is altered. In exp. 3, for example, *L* was at first blocked by *H* at 6 volts; but later, *L* brought responses to maximal and was not affected when *H* was increased to 10 volts though the *H* response rose 30 p.c. In another experiment, with altered connections, *L* came through fully as the voltage of *H* was raised from 20 to 40—the *H* response increasing 70 p.c. over this range. A complete test, altering the duration rather than the voltage of *H*, is shown in Table III.

TABLE III.

	Capacity of <i>H</i> : μF					
	0.1	0.2	0.3	0.4	0.5	0.8
<i>H</i>	15	135	195	210	225	220
<i>L</i>	300	295	300	295	300	305
<i>H</i> + <i>L</i>	290	280	270	270	275	260

H = 10 volts, 250 ω shunt; *L* = 10 volts, 250 ω shunt.

0.1 μF at low speed (600 per sec.) *H* was maximal at 10 volts and 0.1 μF .

It will be noted that, though 0.1 μF gave a maximal response at 600 per sec. it was barely above threshold at higher rates—in this case 1700 per sec. This point will be further substantiated later. Of more immediate concern: *L* comes through the *H* region equally well, and nearly completely as the *H* response increases from threshold to a maximum at 0.5 μF capacity. As the duration of the *H* discharges is still further increased the *H* response remains the same while *L* progressively blocks. In other words, the ability of *H* stimuli to excite (or "inhibit") nerve varies quite separately from their ability to block *L* impulses.

The results so far may be roughly summarized by the statement that low-frequency stimuli applied to a nerve trunk above, below, or at the region of application of high-frequency stimuli of identical character are able to increase responses to maximal, even though the high-frequency responses alone are greatly reduced. This indicates that the high-frequency stimuli are largely failing to excite. On the other hand, the high-frequency region may completely block impulses initiated above it. This is likely to be the case for relatively frequent low-frequency impulses or with moderately injured nerve, and indicates that the high-frequency stimuli may also lead to a local rise of threshold. Further observations with *H* stimuli alone add some information on these points.

In one experiment, the nerve was deliberately injured by tearing the sheath in two lines. The falling off of response with frequency appeared at much lower values than before (Table IV).

TABLE IV.

Stimuli per sec.	Intact Response	p.c.	Injured Response	p.c.
450	252	100	178	100
1060	252	100	119	67
1500	247	98	55	31
2300	163	64	23	13

It has already been pointed out that responses to *H* with cathode proximal are usually much less than with cathode distal, and the result attributed to block at the anode. Yet, an increase in *H* shocks often increases the cathode proximal response. Since the block could hardly become less, this must mean that more fibres are being activated. More direct evidence also shows that stimuli which are maximal at 500 per sec. are definitely submaximal at higher rates—though the individual discharges remain identical. One experiment has been mentioned; another test of *H* strength follows (Table V).

TABLE V.

	Response	Volts	μ F
<i>L</i> (600 per sec.) =	295	—	—
<i>H</i> (660 per sec.) =	275	20	0.1
<i>H</i> (2500 per sec.) =	125	20	0.1
„	110	20	0.5
„	100	20	1.0
„	100	20	2.0
„	190	30	0.1
„	220	40	0.1

In this case, increasing the duration of the *H* shocks (larger capacity) actually gives feebler responses, but increasing intensity (voltage) greatly increases the response. Controls eliminate the possibility of current spread to the galvanometer as an error here. Similarly, with a given *H* stimulus applied over widely separated electrodes—with high nerve resistance—shocks that are maximal at frequencies of 600 are definitely submaximal at 2400, since moving the electrodes closer together may increase the latter response over 50 p.c. It should also be noted in this relation that with the condenser charging as well as discharging through the nerve, so giving alternating shocks at double the ordinary frequency, the response of the nerve is commonly not less but more than for the one-way discharges (see Table II for partial data). (Tests in the stimulating circuit or on the nerve adjacent to the inter-polar stretch failed to show any rectification of the alternate shocks.)

Finally, experiments performed with Dr Bugnard show that at 4° C. the falling off of response with increased frequency begins at about 400 per sec. rather than, as at usual temperatures, at 1000–1500 per sec.

DISCUSSION.

The results speak clearly, then, for a local influence of the high-frequency stimulation of nerve. The stimulation may lead to a diminished conductivity through the exposed region and to a diminished excitability of this region, as in a state of anelectrotomus, or of relative refractoriness. To a large extent, however, the high-frequency shocks are failing to supply adequate excitation. Low-frequency shocks superimposed in the interpolar stretch do evoke a greater response, and this cannot be simply a summation of stimuli effect since it occurs when the two sets of shocks are in opposed directions. The possibility of rapid stimuli evoking a series of very feeble decrementing impulses also would seem to be excluded by these results—for extra impulses set up proximal to the high-frequency region should not get through to increase the total response of a more distal region—as they do.

The high-frequency stimuli, therefore, act locally to render the nerve less irritable and conductive, and at the same time are themselves less than maximally excitant. The first effect recalls the demonstration by Bishop and others that strong induction shocks may cause momentary block by sharply depolarizing the nerve. The second may be related to a distortion of the sharp condenser discharge currents in the nerve itself or to a “smoothing out” in the excitation process.

Though very short current pulses are delivered to the surface of the nerve by the electrodes, these might be flattened and slowed in passing through alternate leaky capacities and conducting fluids on the way to the irritable structures. Even high-frequency (10^5 sec.) sine currents may not excite until ten or more oscillations have passed through a nerve (Gildemeister), which similarly suggests a tissue distortion, or rectification, of the applied currents. More important is a lag in the physiological excitation process itself, which would act in the same way. That a physiological rather than physical “lagging” is crucial is indicated by the marked slowing effect of low temperature, of injury, and of continued activity and equilibration, with a lowering of the critical frequency.¹

¹ In the slower crab nerve, the duration of the excitation process can be strikingly demonstrated. With high voltages and short times, introducing the alternate shocks doubles the nerve response, while with low voltage and long times this abolishes all response [see Gerard, 1934*b*]. The effect of continued activity at low frequency on frog nerve is to slow its reactions markedly, as in extreme equilibration [see Gerard, 1934*a*].

With such a smoothing, then, it is clear that at low frequencies the "excitation state" can rise and fall over a wide range between successive stimuli, whereas at high-frequencies it cannot. If a certain amount of change of excitatory state is "threshold" for excitation, responses to low-frequencies will be maximal, to high ones, submaximal. Similarly, alternating shock direction, even while doubling the total frequency, should give a greater response—as it does. The superposition of a low frequency on a high should stimulate. This is not only a matter of summation of stimuli, since the low-frequency discharges may be opposed in direction to the high ones. Omitting occasional pulses from the high-frequency series should similarly excite—as is the case for a gap in a constant (Lucas) or sine current (Gildemeister). Also, interrupted unidirectional stimuli (iterative) have under proper conditions, a lower threshold than the unbroken constant current [see Lapicque, 1926].

The high-frequency condenser discharges, then, tend to mimic polarizing currents (as do also sine currents)—they alter irritability and conductivity to the extent of block in the extreme; but ordinarily permit the nerve exposed to them to respond to other, less constant, excitation while themselves failing to excite.

Bugnard and Hill [1935] have subsequently (see following paper) performed experiments with the series of shocks at low-frequency interposed at fixed positions, midway between successive shocks of the high-frequency series. In this case no increased response results from adding the low to the high; which excludes our original picture of a relatively very slowly waxing and waning excitatory process. On the other hand, the explanation of Bugnard and Hill, based on a combination of effects (refractory period, summation, recovery interval), is not essentially different from that of a varying state of excitation. Some crucial factor in the nerve is decreased on stimulation, more on high-frequency than slow, and returns progressively towards normal with elapsed time since the last stimulus. A high-frequency keeps recovery at a minimum. [See also Gerard, 1930, p. 506, on the same point]. The particular factor involved may well be the concentration of potassium ions moved to or from the membrane, as has often been surmised [see Gerard, 1930; Bugnard and Hill, 1935]; or, equally well, the concentration of a reacting substance, as phosphagen, balanced between hydrolysis and resynthesis [Gerard, 1934*a*]. The present experiments do not decide; though the extra restoring action of oppositely directed shocks is slightly more suggestive of the first alternative. The effect of injury might likewise be related to the passage of potassium into the intercellular spaces.

SUMMARY.

The diminution of nerve responses to high-frequency condenser discharges (2000 per sec.) as compared with low (500 per sec.), has been analysed by the use of separate high- and low-frequency stimuli applied simultaneously at the same or separate calomel electrodes, using the conducted action potentials as a measure of activity.

In most cases, low-frequency stimuli applied to the nerve trunk above, below or at the region of application of high-frequency stimuli of identical character, are able to bring the response to maximal, even though the response to high-frequency alone is greatly reduced. Under these conditions, the high-frequency is largely failing to excite. Stimuli which are maximal at 600 per sec. may give 3 p.c. responses at 1700 per sec.; but 80 p.c. if the shocks are prolonged eight times. Under other conditions, especially with high-frequency shocks of longer duration, or more frequent low-frequency shocks, the high-frequency is able to block low-frequency impulses passing through the high region. The high-frequency discharges act upon the nerve, then, much like electrotonic currents, to depress or block in extreme cases. Ordinarily, the high-frequency stimuli, while largely failing to excite themselves, do not prevent the full response when low-frequency stimuli or impulses are superimposed.

Some physiological process long outlasts the shock that initiates it; and it is clear that at low-frequencies the excitation state will have ample time to wax and wane, while at high-frequencies it will build up and be maintained with little fluctuation. The further facts that injuring, cooling or equilibrating a nerve by previous activity, all of which slow its reactions, alike lower the frequency needed to give the high-frequency effect speak for this interpretation.

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