ACTION OF DRUGS ON SENSORY NERVE ENDINGS

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This review is primarily concerned with two aspects of the effects of chemicals on sensory endings, namely, the role of a chemical transmitter, and the site of action of chemical substances on sensory endings. Other aspects may be found in excellent reviews by Smith (1) and Zipf (2). Here, the functional definition of a sensory ending will be adopted, i.e., that it consists of two functional parts, the generator region and the regenerative region (3).

Is there a chemical transmitter?—At the Cold Spring Harbor Symposium on sensory receptors (4) a consensus seemed to favor the involvement of a sensory transmitter at mechanoreceptors, as indicated by the support of Grundfest (5) Wersäll et al (6), Flock (7), Davis (8), and Murray (9). But so far there is no proof of its presence or its nature, a position conceded by those favoring the transmitter hypothesis, e.g., Davis (8). Moreover, in the Pacinian corpuscle and the muscle spindle there are good reasons to believe that a transmitter cannot be responsible for producing the generator potential as pointed out by Grundfest (10). For example, the latency between the stimulus and the start of the generator potential is much too small (11–13) being 0.3 msec in the frog's muscle spindle (13) and less than 0.2 msec in the Pacinian corpuscle at room temperature (11). In fact the latency shows hardly any detectable change between 20°C and 40°C (see Fig. 2 in 12).

However in other receptors, notably the vestibular sensory endings, auditory endings, and lateral line organs of fishes (6, 7, 14, 15), the histological relation of the sensory nerve terminals to the hair cells is so like a synapse that it is tempting to think that a transmitter is involved. In addition, Grundfest has encouraged this approach by his hypothesis relating to the excitation of electrically inexcitable membranes (16) which led to his suggestion that the auditory and vestibular endings are stimulated by a chemical transmitter (10, 17). These temptations have persisted because there has been no serious consideration of how the information relating to the movements of the hair cells can be transferred to the generator region by methods not involving a transmitter. One alternative explanation, in the

case of aortic chemoreceptors (18, 19), could be that the generator potential is produced by mechanical deformation of the generator region of the ending. For example, given some rectification by the body of the cell, the sinusoidal pressure changes produced by the vibration of the auditory hair cells could suitably vary the size of the generator potential so that the frequency of discharge is varied with the intensity of the stimulus (20), in accordance with the known relation between the frequency of discharge and the generator potential, as shown by Katz in the muscle spindle (21) (see also 22). It is indeed rather surprising that such possible mechanical processes have not been considered seriously so far, because it is recognized that the hair cells and nerve fibers must follow relatively high frequency pressure changes (17), and so some deformation of the nerve terminals has to take place when the hair vibrates during receipt of auditory stimuli. Moreover, the order of deformation expected should not be far different from that which occurs at the nerve terminal of the Pacinian corpuscle, which responds to vibratory stimuli with a fidelity resembling a seismograph (23, 24) and is therefore likely (under natural conditions) to have a strain sensitivity much less than 100 to 1000 Å, as estimated roughly by Lowenstein (see page 43 in 25).

The case for involvement of a transmitter has gained much support from experiments on the superfused carotid body by Eyzaguirre and his coworkers, who believe that there is a transmitter and it is ACh (26–31). They have studied the effects of many pharmacological agents, and their results support the view that ACh is involved as a transmitter/metabolite in the process of excitation of chemoreceptors. Some of these results need to be re-interpreted since Fidone & Sato (32) have shown that there are baroreceptors with nonmedullated fibers in the sinus nerve, which, not unexpectedly, are also stimulated by chemical substances such as ACh (3). It is noteworthy that the eserinized chemoreceptors can be stimulated by very low concentrations of ACh of the order of 10^{-11} (30). However, the main evidence favoring ACh results from the excitation of the downstream 'in-series' superfused carotid body by ACh liberated by the upstream one when it is made anoxic (27). Serious doubts have been cast on this interpretation, since the upstream carotid body cannot produce the large quantities of Ach needed for stimulating the *uneserinized* downstream carotid body (33).

Two other observations make it unlikely that ACh is the transmitter. First, many chemoreceptors with medullated fibers are not stimulated by ACh (18). Second, cooling greatly reduces or abolishes the excitatory effects of Ach on chemoreceptors that are still responsive to hypoxia (33, 34). Recently Fidone et al (35) and Fidone & Sato (32) have claimed that carotid chemoreceptors with medullated fibers are (unlike aortic ones, 18), more sensitive to ACh than those with nonmedullated fibers. In view of their unusual recording methods (so-called monotopic, which consist of two differential inputs with a common distal electrode) and the short conduction distances involved (about 4 mm), their observations could be subject to very large errors. This has been confirmed in recent experiments (36) in

which, using the recording arrangements employed by Fidone & Sato (32), the conduction velocities of nonmedullated fibers (1–2 m/sec) measured by conventional methods yielded velocities of 10-25 m/sec by their monotopic method. It is therefore possible that some of the endings that were highly sensitive to ACh (32), and which were thought to be connected to medullated fibers, were in fact connected to nonmedullated fibers. Doubts also arise in connection with their observations on the depression of the compound action potential, because such depression could be produced only if the frequency of discharge in the fibers (following chemical stimulation of the receptors) was of the order of 200 to 500 impulses/sec (see page 26 in 37), which is highly unlikely (see Fig. 2B in 32).

Thus there is still no unequivocal evidence to show that ACh or a metabolite that is washed away by the flow of blood might be a chemical transmitter. However, it is still possible that excitatory substances such as cyanide, DNP, and ATP (38–44) might act on chemoreceptor cells in the same way as hypoxia, i.e. by liberating metabolites, other than ACh, that excite the nerve endings (43–46). The metabolite hypothesis was advanced by Neil (47, 48) to explain the excitation of chemoreceptors following hemorrhage, in line with the then prevailing belief originating with Comroe & Schmidt (49) that the oxygen requirements of the chemoreceptors were small. Another point that lent support to the metabolite hypothesis was the general impression (50, 51) originating with Bogue & Stella (52) that the discharge of chemoreceptors continued for as long as 30 min after death. These views are now questionable because Daly et al (53) have demonstrated that the oxygen requirement of the chemoreceptors is quite considerable, and because the discharge in chemoreceptor *single fibers* falls within 2 to 3 min after circulatory arrest (18). The latter evidence does not rule out the existence of a metabolite, but the fact that the discharge produced by anoxia is not increased by circulatory arrest makes the case for a metabolite very weak (18). It therefore follows that substances which excite chemoreceptors probably do so without the intervention of a metabolite and that, like ACh and phenyl diguanide, they probably act on the regenerative region of the ending (see below). An example of such a substance is sodium cyanide, which is used as a stimulant of arterial chemoreceptors. It is not absolutely specific because it also stimulates some gastric stretch receptors in doses that are excitatory for arterial chemoreceptors (36). The same must apply to the many substances used hitherto (e.g. see 42, 46), including ATP.

Here Duncan's hypothesis concerning the role of ATP in the process of impulse generation should be considered (54, 55). Duncan has proposed that the mechanism underlying the generator process at sensory endings is similar to the mechanism used by the amoeba in sensing mechanical stimuli, i.e., there is an enzyme (ATPase) located on the membrane which can be pushed into contact with the substrate (55). Duncan has provided many examples aimed at demonstrating the universal role of ATP at sensory endings (54, 55), but not all are acceptable. For example, it is claimed that

ATP stimulates carotid baroreceptors (41); this has not been confirmed by Joels (56). It is likely that other receptors are also not stimulated.

Site of action.—The hypothesis that the observed effects of chemical substances are due to their action on the regenerative region of the ending (rather than on the generator region) was based largely on the known effects of procaine and the effects of veratrum alkaloids whose action on the sensory endings could be explained by their known effects on medullated fibers (3, 57). The greater responsiveness of endings of nonmedullated fibers (as compared to those with medullated fibers) was attributed to the greater responsiveness of the regenerative regions of endings of nonmedullated fibers to the chemical substances. Good evidence in support of this hypothesis has since been obtained using ACh and phenyldiguanide (18) on aortic chemoreceptors, which are the only known endings with adequate numbers of both medullated and nonmedullated fibers (58). Further evidence in support of this hypothesis has been provided by Ottoson (59) (see below) who used the frog muscle spindle in which the intrafusal fibers had apparently been destroyed. Before dealing with this evidence it should be pointed out that ACh even in concentrations of 10^{-3} did not stimulate the ending (59). This is consistent with the earlier conclusion of Hunt that ACh stimulates the muscle spindle by causing contractions of the intrafusal muscle fibers (60). It is also consistent with the conclusion (3) that ACh does not stimulate *directly* certain endings of medullated fibers, e.g., pulmonary stretch receptors (61), and perhaps also cutaneous receptors (62). Nor, as expected, does it stimulate the aortic baroreceptors with medullated fibers in vivo in doses of 100 to 300 μg (36) which are adequate for producing a profound discharge in chemoreceptors. This contrasts with the excitatory effect of ACh on carotid baroreceptors in vitro, but here certain other points (see 3) are pertinent. For instance, some of the carotid baroreceptor fibers from which impulses were recorded (63) could have been nonmedullated (32), in which case stimulation by ACh would be expected (3).

In contrast to ACh, certain anticholinesterases, e.g., eserine, DFP, and mintacol (but not prostigmine) stimulated the muscle spindle markedly (59). Typically Ottoson observed marked stimulation with DFP but he made no comments on the site of action of these substances. However, it is clear from the published records (see Fig. 5 in 59) that the excitatory effect was produced without any increase in the generator potential. In the case of mintacol (3×10^{-6}) there is a small d.c. shift, but this is far too small to account for the profound excitatory effect (Fig. 5 in 59). Similarly, Ottoson found that the stretch-induced generator potential was not increased after these substances. These results therefore show that the excitatory effect must have been produced by an action on the regenerative region, presumably by increasing its sodium permeability, as is known to occur with veratridine (64).

Even more convincing evidence has been provided by Wellhöner (65) who studied the effect of aconitine on the crayfish stretch receptor primarily

to test Paintal's hypothesis (3). From the evidence, which is unequivocal, Wellhöner concluded that aconitine stimulated the receptor by acting on the regenerative region. It is likely that this effect is due to an increase in sodium permeability of the regenerative membrane elements (65). It is reasonable to conclude that in the case of other endings studied by Wellhöner, such as pulmonary stretch receptors (66), atrial type B, and ventricular pressure receptors (67), the mode of action is the same. Recently Wellhöner has recorded similar effects of delphinin and andromedotoxin on pulmonary stretch receptors (68). It may be presumed that the mode of action of these substances is also the same, i.e., like veratridine. It was concluded earlier (3) that veratridine acts on the regenerative region and not on the generator region of the ending. Strong support for this conclusion has been provided very recently by Wellhöner, who has found that veratridine has no effect on the generator potential of crayfish stretch receptors even in a concentration 600 times greater than that effective for stimulating or sensitizing the receptor (69).

Wellhöner could block impulse initiation and the actions of aconitine (65) and veratridine (69) on the crayfish stretch receptor by the addition of 10^{-8}–10^{-7} g/ml tetrodotoxin to the bath. Concentrations of tetrodotoxin 10 to 100 times greater leave the generator potential unaffected (65, 69, 70). This is in agreement with the earlier results reported by Loewenstein et al on this receptor (71). Similar results were obtained in the Pacinian corpuscle, where the stimulus—generator potential relationship was unaltered after tetrodotoxin although regenerative activity had ceased (71). Ozeki & Sato (72) and Nishi & Sato (73) found that lower concentrations were effective. In addition Nishi & Sato (73) found that the amplitude of the generator potential of the Pacinian corpuscle fell after about 30 min following application of tetrodotoxin. This reduction, which amounted to about 40%, was not enhanced by further addition of tetrodotoxin. They speculated on the mechanism that could bring about this reduction in the generator potential in relation to the effects of sodium-free solutions, which are well known for blocking the regenerative mechanism in Pacinian corpuscles and frog's muscle spindle, long before any demonstrable change in the generator process becomes visible (21, 74–78).

On the other hand, Ottoson et al (78) found that tetrodotoxin did not alter the generator potential of the muscle spindle even in a concentration 50 times that required to block regenerative activity. They concluded that since tetrodotoxin was unable to block the depressant effects of sodium-free solutions, the sodium carrier system of the generator membrane is different from the sodium carrier mechanism of the regenerative membrane (78). They found that increasing calcium concentration retarded the effects of tetrodotoxin on regenerative activity, and eliminating calcium reduced the generator potential still further (about 20%) after it had been reduced to about half by sodium-free solutions. This indicates that calcium ions are directly or indirectly responsible for part of the generator potential, although there is no evidence that this would happen in the presence of so-

dium. This depression of the generator potential by calcium-free media has to be kept in mind while considering its excitatory effect on the muscle spindle (79, 80). Clearly such effects are due to an action on the regenerative region. So are the effects of changes in osmotic pressure of the solutions bathing the muscle spindle (81).

Effect of anoxia.—Considering the relatively greater resistance of the generator mechanism to chemical substances it is not surprising that it is also more resistant to anoxia than the regenerative mechanism. This was first clearly demonstrated by the fact that (following asphyxia and circulatory arrest) antidromic impulses are blocked in the mammalian muscle spindle at a time when naturally evoked orthodromic impulses continued to be produced even for considerable periods after block of the antidromic impulse either in the generator region or at the first node (82). This is also true in the insect mechanoreceptor in which, as shown by Thurm (83), the generator potential survives during anoxia after the impulses have been abolished. This might also be true for the visual system in which the late receptor potential survives for over 8 minutes after circulatory arrest (see Fig. 10 in 84). However, the early receptor potential [which is not a generator potential but a receptor potential, according to Davis's terminology (85)] is even more dramatic in its resistance to anoxia (84, 86). Telelogically one should expect the generator mechanism of the aortic and carotid chemoreceptors also to be relatively more resistant (than the regenerative region) to anoxia, since they are maximally stimulated during anoxia.

Effect of reduced temperatures.—There is an impression that the temperature coefficient of the generator mechanism is high (12, 54). This has arisen from the observation that the Q_{10} for the amplitude of the generator potential of the Pacinian corpuscle is about 2 (12, 87), which is true only at temperatures below 25°C. However, since this is a mammalian preparation it is perhaps more relevant to consider the Q_{10} between 25 to 40°C. At this range the Q_{10} is 1.4 to 1.6 (See Fig. 3 in 12 and Table 1 in 87). These values cannot be regarded as high. Moreover, in the frog's muscle spindle lowering the temperature below 20°C does not reduce the amplitude of either the dynamic or static generator potential (88). But the frequency of discharge is reduced, the Q_{10} for this being about 2, which is similar to the value reported earlier by Matthews (89). Ottoson's observations lead to the inference that the effect of reduced temperature must operate through an action on the regenerative region, possibly by slowing the recovery processes, since the size of the generator potential is not decreased. The Q_{10} for the ARP of frog's fibers as estimated from the results of Schoepfle & Erlanger (90) is 3.0 between 20 and 10°C. This could account for the reduction in the frequency of discharge (88, 89), since the Q_{10} for the relative refractory period (e.g. at 40% recovery) is the same as that for the absolute refractory period (91).

The observations on the muscle spindle (88) are in conformity with

those of Burkhardt on the crayfish stretch receptor, who found that not only did the generator potential not fall, but it actually increased with reduction in temperature (92). It is necessary to account for the difference between the effects of temperature on the amplitude of the generator potential of the Pacinian corpuscle (Q_{10}=1.4–1.6) with those on the muscle spindle (Q_{10} = 1.0). But in any case it can be concluded that the generator region is more resistant to cooling than the regenerative region (with a Q_{10} of about 3 for the ARP), which is in keeping with the fact that it is also relatively more resistant to anoxia and chemical substances than the regenerative region.

Effects on accessory structures.—It appears that the accessory sensory structures and the associated physiological processes are hardly, if at all, affected by lowering the temperature. This appears to be so in the aortic chemoreceptors in which the pO_2 sensor (see 18) has a Q_{10} close to unity (34). The pO_2 sensor performs the same type of function as the capsule of the Pacinian corpuscle (or similar structures in other sensory receptors, e.g., muscle spindle or poorly defined structures as in the case of arterial baroreceptors and especially in the case of endings of numerous nonmedullated fibers where the fibroelastic tissue surrounding the free nerve ending probably serves the function of the accessory structure). It will not be surprising to find that these fibro-elastic or other structures are practically unaffected by lowering the temperature, as revealed by the fact that the Q_{10} for the generator potential of the denuded Pacinian corpuscle is the same as that of the intact one (12).

It has been suggested that the pO_2 sensor of the aortic chemoreceptors serves to meter the local pO_2 (18). It appears that the accessory structure of the Pacinian corpuscle and the corresponding structures or elements in the case of other sensory receptors, like the pO_2 sensor of chemoreceptors, apart from acting as filters of the stimulus (e.g. see 93), constitute the actual meters for the intensity of the stimuli. These sensory meters are not only practically unaffected by changes in temperature, but they also seem to be unaffected by chemical substances that affect the regenerative and generator regions of the receptors. This has been tacitly assumed so far in all investigations on the effects of chemical substances on sensory endings. Actually, the resistance of sensory meters to changes in temperature and chemical substances is probably quite dramatic. For instance one would not be surprised if the functions of the sensory meter of the Pacinian corpuscle (i.e. capsule) survived, at least briefly, in the presence of 0.33M formaldehyde, as does the early receptor potential (94), which not only survives anoxia (84, 86) but also at temperatures below 0°C (95, 96).

Thus it appears that there is an increasing order of resistance to fall in temperature, anoxia, and chemical substances as one proceeds backwards from the regenerative region to the stimulus as shown in Figure 1. Several conclusions follow from this scheme. For example, it follows that the vestibular hair cells and the hair cells of the organ of corti must serve as sen-

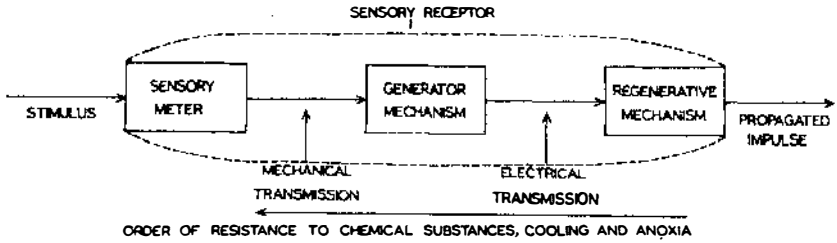

FIG. 1. Mechanisms involved in the excitation of sensory receptors, and their relative resistance to chemical substances, cooling, and anoxia.

sory meters. They should therefore have a Q_{10} close to unity, should be relatively resistant to chemical substances, and should be able to function during anoxia for at least some time after all impulses or generator potentials have ceased to be generated. It might be argued that this is unlikely because the hair cell with its nucleus and cytoplasmic contents must be metabolically active. This cannot be doubted, but it is also possible that the function of the cell is mainly to ensure maintenance and repair of the hairs of the cell, so that so long as the hairs and the associated elements are intact, the mechanical deformation of the generator region at the base of the hair cell can take place without being influenced by other factors such as anoxia and temperature.

Concluding remarks.—Quite rightly, owing to the absence of direct evidence on the effects of excitatory substances on the generator potential, the hypothesis that chemical substances produce their effects on mechanoreceptors by actions on the regenerative region (3) appeared to be acceptable with reservations a few years ago (e.g. see 1). Since then, the required evidence on the generator potential of mechanoreceptors has become available, and there can be little doubt now regarding the above hypothesis which is also applicable to arterial chemoreceptors. This view is consistent with the fact that not only is the generator region of the ending more resistant to chemical substances, but it is also more resistant to anoxia and cooling than the regenerative region. However, the most resistant structures appear to be the sensory meters which are the accessory cells or structures or poorly defined fibro-elastic elements in which lie many receptors, e.g. baroreceptors, cutaneous receptors. These sensory meters (in addition to filtering the stimulus) transmit, by mechanical deformation, information regarding the intensity of the filtered stimulus to the generator region of the ending, apparently without being influenced by anoxia, chemical substances, or changes in temperature (Fig. 1). Mechanical deformation of the generator region could be the rule even in receptors other than mechanoreceptors, because if the generator membrane is electrically inexcitable (5), and there is no chemical transmitter, then we are left with only mechanical transmission, e.g., as postulated in the case of arterial chemoreceptors (18). The

fact that the generator mechanism is relatively resistant to chemical substances does weaken the case for a chemical transmitter.

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