The Mechanisms of General Anesthesia

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The general anesthetics make up a class of compounds, grouped not because of what they are but because of what they do. The practical necessity of stressing differences among anesthetics tends to submerge the extraordinary fact that this diverse group has an even larger number of effects in common. The common property of these compounds is that they all set off a profound reorganization of the nervous system into a series of states grouped under the term "general anesthesia," varying from light to deep anesthesia. I maintain that, if the various states are described in sufficiently broad categories, the sequence from loss of consciousness to arrest of respiration is the same whatever agent is used. This does not mean that, if the sequence is examined in detail, important differences will be observed. However, no matter how the phenomenon of a dose-related depth of anesthesia is described, the fact remains that the general anesthetics produce the same sequence of coordinated changes in nervous activity, no matter which drug is employed, provided that their central concentrations are slowly raised. The dose-related effect of such a large group of compounds poses the main question in explaining the mechanism of general anesthesia, and the question becomes more meaningful when one adds that there is another diverse group of compounds that imitate some aspects of anesthesia without producing the whole pattern; in this class I would include morphine and chloralose. The sequential concatenations of different patterns of excitability of different parts of the central and autonomic nervous systems cannot, however, be used to diagnose which compound is being used to induce general anesthesia.

The Nature of Theories

The first part of the question on the mechanism of central effects of general anesthetics is to ask if these different compounds produce their effect by the same mechanism. Since the drugs effect a complex sequential pattern of changes, it would seem at first that such a series could only be explained by a single mechanism. Unitary explanations have been attempted many times since the problem first arose. These explanations involve correlating some physical or chemical property of the various species of molecules with their anesthetic effectiveness. One group of theories deals with effects on enzymatic reactions in oxidative metabolism and has been reviewed and criticized recently by Bunker and Vandam.¹

A recent and spectacular attempt at a correlation between anesthetic effect and physical properties has been that of Pauling.⁶ This theory, which is limited to the non-hydrogen bonding agents, does not purport to have anything to say about such compounds as the barbiturates. The theory suggests that anesthetic gases, including the inert gases such as xenon, are acting by an effect on hydrate crystals. Pauling, with characteristic honesty, provides a caution about his own theory and by implication about other theories of this type. He says, "The striking correlation between the narcotizing partial pressure of the anesthetic gases and the partial pressure necessary to cause formation of hydrate crystals provides some support for the proposed theory, but it is recognized that any theory based upon the van der Waal's attraction of the molecules of the anesthetic agent for other molecules would

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show a similar correlation, inasmuch as the energy of intermolecular attraction is approximately proportional to the polarizability (mole refraction) of the molecules of the anesthetic agent."

A third ingenious attempt at a single action theory represents a sophisticated extension of the Meyer-Overton theory of lipid solubility and surface effects. These authors suggest that both barbiturates and cocaine may have similar steric interferences when incorporated into the lipid component of membrane, so that ionic binding is changed. It would be a discovery of major importance if it were found true that barbiturate and cocaine-like compounds had a common target mode of action but this finding would not necessarily explain why argon is also a general anesthetic.

The failure of attempts to develop a single mechanism-theory does not mean that no such theory is possible. In view of the failure so far, perhaps the time has come to ask if a multiple mechanism-theory could be developed which would explain how the same complex pattern of results could be produced by entirely different mechanisms.

The Blood-Brain Barrier

First, let us consider the possibility that the sequence of sensitivities is not a property of the nerve cells or of the anesthetics but the result of a selective admission of the substance from the blood stream to the central nervous system. There is no doubt that there is an extremely powerful and effective blood-brain barrier. It is not certain that any substance, even water, moves passively down its concentration gradient from blood to intraneuronal cytoplasm. One example of the differential effectiveness of anesthetics is that spontaneous activity of cells in the cortex ceases at a much lower blood concentration than does the ongoing activity of respiratory cells in the medulla. If this aspect of anesthesia were to be attributed to a differential effect of the blood-brain barrier, it would be necessary to postulate a barrier differentially effective against the full range of anesthetics. In addition to postulating such a remarkable universal barrier, it would be necessary to suggest that the barrier was more leaky in the cortex than in the medulla. The facts suggest that, if there is a difference, it is the other way around. The area postrema directly adjacent to the respiratory neurons is one of the regions where a leaky barrier exists; hydrogen ions and carbon dioxide in the blood appear to have an unusually direct access to the region of the respiratory neurons. Furthermore, a blood-brain-barrier theory of differential sensitivity would have to explain why the effect is seen not only with the presence of a new compound but also with the disappearance of an old one such as oxygen. The blood-brain barrier seems an unlikely cause of differential sensitivity. Fortunately three newer techniques labelled anesthetics, local perfusion, microelectrophoresis, will allow a direct examination of this question.

The Synapse

If the sequential effects cannot be attributed to the blood-brain barrier, one must turn to the nerve cells themselves. It has been generally agreed for some time that anesthetics were having their effect in the synaptic region rather than axons. The success or failure of impulse transmission from the axons of convergent afferent fibers into the efferent axon of a cell is now recognized to be made up of a considerable chain of events. Anesthetics might affect one or many of these links. Studies have already been reported on the differential effect of anesthetics at various points in the linkage and it is evident that some affect one point and others other points (Somjen 1966 elsewhere in this symposium). The known or suspected points at which synaptic transmission may be affected are:

1. Impulse transmission in the incoming axons
   A. Blockade
   B. Depolarization
   C. Hyperpolarization

2. Repetitive firing in the terminal arborization

3. Chemical transmission at junction points
   A. Synthesis
   B. Release
   C. Transfer
   D. Reception

4. Electrical transmission at junction points
   A. Release (Presynaptic membrane properties)
   B. Transfer (Extracellular impedance)
   C. Reception (Postsynaptic membrane properties)
5. Propagation from contact point to axon hillock
   A. Electrotoneic
   B. Impulses travelling in dendrites

6. Threshold variation at points of impulse initiation

7. Repetitive postsynaptic firing
   A. Generated by bombardment of external origin
   B. Generated by intracellular mechanism

These seven stages or components of synaptic transmission are subject to control and therefore the overall set of these links determines the input-output characteristics of each synapse.

An Example From the Spinal Cord. The dorsal horn of the spinal cord has been particularly intensively studied. Rexed recognized 6 horizontal laminae in dorsal horn of cat spinal cord. Lamina 1 is the thin layer of marginal cells. Laminae 2 and 3 contain three components, the small cells of substantia gelatinosa, the terminations of entering fibers of cutaneous origin and the dendrites of deeper cells whose cell bodies lie in lamina 4. Lamina 4 contains the most dorsal large cells. Lamina 5 lies across the narrowest portion, the neck, of the dorsal horn. Lamina 6 exists only in the lumbar and cervical enlargements and occupies the most ventral part of the dorsal horn.

For some years we have made a study of the factors which control transmission across the cells of laminae 4, 6, 7, 15-16. The cells in this lamina receive monosynaptically many different types of cutaneous myelinated fibers and the majority are also fired by C fibers. They have relatively small peripheral receptive fields. We know that a presynaptic gate control mechanism affects the transmission of impulses out of the presynaptic terminal arborization onto the cell bodies. The cells operating this gate control seem to be the small cells of the substantia gelatinosa. They operate by way of axo-axonal contacts on the terminals of the entering fibers. These contacts control the membrane potential of the terminals which in turn determines the postsynaptic effectiveness of impulses entering the terminals. We know of at least three factors which affect the set of this gate control mechanism. One is the relative balance of activity in large versus small diameter peripheral afferents. If the majority of incoming activity is in large diameter fibers, the endings are depolarized and the gate moves to a partially closed position. On the other hand, if the activity is predominantly in smaller A fibers and C fibers, the terminals hyperpolarize and entering impulses become more effective. The other two factors which control the set of this gate are impulses descending from the brain stem and from the pyramidal tract. The discovery of this gate control led to a new theory of pain mechanisms. Once the afferent impulses have penetrated across the junctional region, there is evidence that they set off propagated impulses in dendrites which travel toward the cell body and there trigger off impulses in the axon. There are also postsynaptic inhibitory mechanisms.

Each cell in lamina 4 has a clearly defined cutaneous excitatory receptive field. Bending hairs, pressure on the skin or cooling within the receptive field cause the cell to discharge. Electrical stimulation of the skin or a cutaneous nerve produces a burst of repetitive firing in the cell. If the afferent volley is restricted to the largest A fibers, the repetitive discharge outlasts the period of arrival of afferent impulses and is succeeded by a period of profound inhibition, at least part of which can be attributed to the closure of the presynaptic gate. If the afferent volley is restricted to C fibers, the cell again discharges repetitively but this time the discharge is followed by a long period of facilitation so that each succeeding afferent volley produces a more and more intense and prolonged period of repetitive firing.

Let us take such a cell and observe what happens when barbiturate is administered. The method of recording is shown in figure 1. In figure 2 the discharge of one cell to an afferent volley generated in the large A fibers from the sural nerve is shown. There is a delay between the stimulus and the first response of the cell caused by peripheral conduction and synaptic transmission times. The cell then responds with a burst of ten impulses. If no anesthetic had been given, this pattern would have repeated exactly with each stimulus which was given every second. The normal anesthetic dose of nembutal for a cat is 25 mg./kg. given intravenously. In this ex-
Fig. 1. Method of generating a display of changes in time pattern of nerve impulses. The processing is carried out in the three stages shown here. The top trace is a diagram of a conventional oscilloscope trace with a stimulus given on the left and single nerve impulses recorded on the right. Each nerve impulse and the stimulus artifact are marked automatically by a small brightening pulse. The second stage shown in the middle line is to reduce the vertical gain to zero. The time of occurrence of the stimulus and impulses is still shown by the brighter dots. The third stage shown on the lower line is to reduce the brightness so that only the dots appear. Now each succeeding sweep with its associated dots is displayed on the screen with a slight displacement above the previous sweep. In this way vertical lines are generated which show the change in pattern of discharge with each succeeding stimulus.

Experiment 50 mg./kg. was infused in three minutes. The ongoing spontaneous activity disappeared after 10 mg./kg. had been injected. When about 15 mg./kg. had been injected the last components of the repetitive discharge began to fail. It will be noted that the latency of each component of the discharge slightly prolongs before it fails. It is obvious that the first impulse has the least variation of latency and the greatest resistance to anesthesia. It is also clear that the last discharge in the burst has the lowest reliability without anesthesia, the greatest variability of latency, and the greatest sensitivity to anesthesia. It is evident that anesthesia is not a switch but has a different effect on different components of the discharge. After a dose of 25 mg./kg., the size of the cell's receptive field to light brushing is unaffected. The effect of C volleys is completely abolished. The presynaptic gate mechanism can no longer be opened by small fiber afferents while the large afferents retain an ability to close the gate without competition from the smaller fibers. The cell retains its ability to respond to light peripheral pressure stimuli but if the intensity of pressure is increased the firing of the cell now fails to signal the increasing afferent volley so that their dynamic range is restricted. The region from which the suspected dendritic spikes can be recorded moves down out of the distal dendrites toward the cell body. Anesthesia has restricted the operating range of the cell certainly by affecting the presynaptic control mechanism and probably also by postsynaptic effects.

In lamina II the cells are also affected by cutaneous afferents and seem to be fired by cells in lamina II. They have larger cutaneous receptive fields and longer latencies than the more dorsal cells. They are also controlled by pyramidal tract and by impulses from the brain stem. They have a particularly interesting

Fig. 2. Progressive failure of a single cell's repetitive discharge during anesthesia. The unit was recorded by an extracellular microelectrode in lamina four of the dorsal horn in an unanaesthetized spinal cat. A stimulus was applied once every two seconds to the sural nerve. Before anesthesia, this stimulus produced a regularly repeated repetitive discharge containing ten impulses. Succeeding repetitive trains are shown placed one above the other by the display shown in figure I. Starting at the bottom of the straight line on the left and continuing for the three minutes represented by the length of the line, a total of 50 mg. per kilogram was injected at a steady rate. It will be seen that the later components of the repetitive discharge fail at lower doses of anesthetic than do the earlier components. It will also be noted that before failure there is a prolongation of the latency of each component. Horizontal time marks are 2 msec.; vertical time line, 3 min.
new property of “novelty detection.” They habituate rapidly to repeated light stimuli in one part of their receptive fields but, if the stimulus point is moved to a new point, they immediately respond briskly. Heavy stimuli override this habituation. The responses of these cells to natural stimuli are abolished by the standard dose of nembutal, 25 mg./kg. intravenous, while electrical stimuli of peripheral nerves continue to produce brisk responses in these cells. In lamina 6, cells respond to passive movements of the ipsilateral leg, have peripheral cutaneous receptive fields, show “novelty detection,” and are strongly affected by descending fibers from the brain stem and pyramidal tract. The most striking property of these cells is that their modality can be switched by the descending systems. In the decerebrate animal, the cells are dominated by their proprioceptive inputs but if the descending impulses are blocked by the localized cold block on thoracic spinal cord, the cells now become dominated by their cutaneous input. Intravenous injection of 25 mg./kg. nembutal abolishes all of these interesting responses to natural peripheral stimuli and the cells responding in a nonspecific and truncated fashion only when hammered by the synchronous afferent volleys generated by electrical stimulation of peripheral nerves.

Toward a Theory. There are three ways in which anesthetics might be acting: (1) by decreasing the excitatory effect of individual impulses, (2) by increasing the inhibitory effect of individual impulses, or (3) by disorganizing the spatial and temporal pattern of bombardment. These are not alternative modes of action; all three may be found to occur simultaneously. We have shown that nembutal has a preferential effect in abolishing a presynaptic facilitating mechanism, leaving full rein to an inhibitory process. This does not mean that this is the only or even the major effect of nembutal on this synapse, since there are also postsynaptic effects.

Certain features of transmission at a single synapse are more sensitive to anesthesia than others. Spontaneous ongoing activity disappeared at lower doses than did the late components of the repetitive afterdischarge. These in turn were more sensitive than the early components. The latency of firing of a particular impulse in the train was more sensitive than was the presence or absence of that impulse. What conclusions is one to draw from this differential dose-related sensitivity of different aspects of synaptic transmission? Surely it would be ridiculous to postulate a different mechanism for each of the observed components. It may well be that the “spontaneous” impulses are generated in a different part of the cell from the evoked impulses. However, it would seem highly unlikely that the barbiturate reached that part of the cell in higher concentration than other parts of the synaptic mechanism or that that part of the cell was specifically highly sensitive. It becomes even more ridiculous if one were to postulate spatially separated and independently sensitive loci on the cell for the generation of each member of the train of repetitive impulses. Let us turn instead to the suggestion that the various components of the output of the cell are set off by inputs which exceed threshold in varying degrees. One would guess that the ongoing spontaneous discharge of the cell is set off by the occasional coincidence of randomly distributed bombarding impulses. The chances of coincidence at the same time and place of 2, 3, 4, 5, etc., impulses becomes very sharply less and less likely as the number of required impulses needed to supersede the threshold increases. Therefore any influence which decreases the input-output relation of the cell will easily abolish spontaneous activity. All synaptic processes are analogue processes, not “all or none” processes. Any agent which weakens any one of the various links in the excitatory chain will have precisely the same effect in abolishing spontaneous activity. It may well turn out that some anesthetics have a predominately presynaptic effect while others may tend to stabilize the postsynaptic membrane. It would not matter where it was active or on which process, one would still expect the most sensitive aspect of the firing of the cell would be that part where the threshold was just reached by the occasional coincidence of independently generated randomly distributed afferent bombardment. Consider now the other extreme, which was the first impulse generated
in the repetitive burst which could only be abolished by a much higher anesthetic dose. One may guess that this impulse was initiated by a grossly supramaximal incoming barrage in which many, perhaps hundreds, of afferent impulses combined to produce a postsynaptic explosion. It is suggested, then, that the differential sensitivity of the different parts of synaptic action may tell one nothing of the locus or mode of action of the anesthetic agent. Precisely the same sequence of effects would be expected, no matter whether the agent had its effects mainly on the terminal arborization of afferents or mainly on the axon hillock of the efferent cell or somewhere in between. The sequence of effects may be an indication of the nature of convergence on the cell and a test of the various safety factors of transmission.

If the degree of spatial and temporal summation of impulses is a major factor in determining degrees of resistance to anesthesia, it is reasonable to ask what factors control the amount of this summation. One important factor is the manner in which the afferent volley is generated. A lightly anesthetized animals retains its tendon reflexes at a time when the flexor reflex can no longer be elicited. The tendon tap delivers a relatively synchronous volley to one synapse. The pressure stimulus delivers a desynchronized volley which is further desynchronized by passage over a series of depressed synaptic links and therefore cannot summate up to a level to overcome the raised threshold of the flexor motoneurons. A practical example of the same type of phenomenon is to be seen in the search for a test which would allow a clinical trial of analgesics. Doses of morphine, for example, which produce a satisfactory response in patients suffering from various pains, had little or no effect on experimental pains set off by electrical stimulation of skin or by rapidly rising skin temperatures. Beecher has reported a test whose results match clinical observations, using ischemic pain. One may guess that the previous tests, by generating highly synchronous massive input volleys, were able to overwhelm partially depressed central synapses even though these same synapses were unable to transmit the asynchronous barrage delivered by Beecher's test or by those pain-producing disorders for which analgesics are effective. The fact that an analgesic dose of morphine does not allay the pain of trigeminal neuralgia or of a skin incision does not mean that morphine does not affect the cells over which the impulses pass. It means that the barrage remains sufficiently intense to jump the raised threshold.

The anatomy of central terminal arbors, a subject about which little is known, is likely to be an important factor in controlling spatial summation of arriving impulses. If an axon branches profusely and many of these branches end on the same cell, then the postsynaptic effect of one arriving impulse will be duplicated many times and the safety factor correspondingly raised. Another method of achieving such multiplication is by mechanisms of repetitive firing which may exist both presynaptically and postsynaptically. We know little of such mechanisms of ensuring the success of synaptic bombardment beyond the fact that they exist. It may be, for example, that the anatomy of interconnection between cells in the respiratory nuclei ensures a massive bombardment of the cells so that excitation and inhibition are alternately grossly supramaximal.

In summary, we suggest that the apparent similarity of the effect of various anesthetics may not be a reflection of identical modes of action of all anesthetics but rather a reflection of the varying stability of different synapses. In particular, we have pointed to factors of anatomy and physiology which may confer a relative resistance of some structures to anesthesia by virtue of the differing levels of supramaximal temporal and spatial summation. The location and mode of action of anesthetics on various aspects of the synapse may differ between anesthetics but the sequence of structures which are affected can be determined by the synaptic organization of the structure rather than by the mode of action of the anesthetics.

References


DISCUSSION

Dr. Somjen: I should like to thank Dr. Wall for an excellent introduction to the remainder of this conference; he has made my job of tomorrow very much easier. I agree with almost everything Dr. Wall has said, but would like to interject two footnotes. First, concerning the relationship between efficiency of synaptic transmission, and vulnerability to anesthetics. There certainly seems to be a true relationship in this respect, in a number of systems. One example is the remarkable stability of the respiratory cycle; it is indeed fortunate that this neural mechanism is resistant to depressant drugs. Other examples may be found in the beautiful quantitative studies of McIntyre and his school. Employing the input-output technique, they have shown the striking differences of efficiency of transmission of different synaptic systems. Often efficiency of transmission is correlated with resistance to anesthetic depression: the more powerful synapses are more difficult to depress. (McIntyre, In: Curtis and McIntyre: Studies in Physiology, p. 199, 1965.) There are exceptions, however. With Dr. Henneman we found instances of this. (Somjen, Henneman, and Carpenter: J. Pharmacol. 148: 380, 1965.) Tomorrow I will show you how the relative efficiency of transmission may be completely reversed during induction of anesthesia. The other point I want to raise concerns the problem whether all anesthetics act basically in the same way; I believe that may be so, at least for many drugs. I believe however that there are quantitative differences, even among closely related compounds. These differences may turn out to be the key as to why one drug is useful in a particular situation, and another drug not.

Dr. Galindo: You mentioned a spinal preparation to which you give a barbiturate and an anesthetic dose, I would be interested to know the criteria for the anesthetic dose? Second, with reference to the theory of pain mechanisms that you proposed with Dr. Melzak (in Science) which is an interesting working hypothesis (we are surely going to hear more about that), but it seems to me that you go a little bit too fast, especially with the effect of the barbiturates. You mentioned that a very small dose of anesthetic will stimulate the inhibitions that you propose. I wonder what this small dose does in suppressing pain in the intact animal, because the barbiturates don’t work that way. On the other hand, you mentioned that large doses of barbiturate are needed to depress the posterior roots; I would like to see the comparison of doses. What is the dose that stimulates the inhibition and what does it do to the posterior roots and their transmission.

Dr. Wall: You and Dr. Somjen are pointing out something that is obviously true. I am not a pharmacologist. I am simply asking that one should not forget the general properties of all anesthetics, while concentrating on the important differences among them. You feel that Melzak and I have gone too fast. We proposed one theory to stimulate discussion and experiment.
One of the many things I have learned from Sir John Eccles is, that if you are going to stick your neck out, take your shirt off and make it perfectly clear that you are sticking your neck out. To answer your question specifically, there is always an untested assumption in talking about anesthetic doses given to acute physiological preparations. One assumes that the dose per kg. which will produce light anesthesia in an intact animal, has the same effect on the spinal cord of an acute spinal animal as it does in the intact animal. Taking that caveat into consideration, I say that one of the effects of a light dose of pentobarbital, 25 mg./kg. intravenously, is to abolish presynaptic facilitation. I am not claiming that the barbiturate is an analgesic because at that dosage barbiturate is producing the whole complex of effects called light anesthesia. If a drug were to be found which specifically abolished the afferent presynaptic facilitation without other central effects, then I would predict it would be an analgesic. To answer your question about the effect of high doses, we have found that pentobarbital 75 mg./kg. intravenously will abolish all signs of unit firing in the large cells of the dorsal horn; yet the negative dorsal root potential is still generated, although its amplitude is reduced. This suggests that the mechanism for the generation of presynaptic inhibition is extremely resistant to barbiturate anesthesia.