Effects of Anesthetics on Spinal Cord of Mammals

G. Somjen, M.D.*

For many years the spinal cord has provided a convenient testing ground for ideas concerning the function of the central nervous system (CNS), and the mode of action of centrally acting drugs. Thus, while discussing the effects of general anesthetics on the cord, we really have our eyes on the brain. In so doing we imply that certain principles of function and organization are common throughout nervous tissue of mammals, an assumption that may not be true in every detail.

With regard to centrally depressant drugs, two related general questions may be raised; one concerns selectivity; the other, the mode of action. Perhaps all depressant drugs exert general effects, but certainly some are more prevailing than others. Given a high enough concentration, excitability and conduction in nerve fibers can be blocked in vitro by any of these agents. With the dosage used in surgical anesthesia, peripheral nerves continue to conduct normally, and so do the long fiber tracts of the CNS. Whether or not the tenuous ramifications of axons in neuropile and at synaptic endings function in a normal way during general anesthesia is not certain. We shall examine this problem in the next section. However, the main depressant action is believed to occur at transmission of excitation across synaptic junctions. A first question is—which synaptic junctions, and the second, by what means? Let us turn to the latter of these questions, mainly because we have more exact information on it.

Mechanism of Synaptic Block during General Anesthesia

Synaptic potentials. If one records excitatory post-synaptic potentials (EPSPs) from a ventral horn cell, and allows the animal to inhale diethyl ether, the amplitude of the EPSP is seen to diminish (fig. 1). This effect is reproducible and reversible. Similar observations were made by Lövning et al., who used thiopental, and by Shapovalov, with pentobarbital. Using extracellular leads in ventral roots we found the same response with thiopental. There is a precise relationship between the depression of the EPSP recorded from one cell, and the depression of the reflex discharge of the population to which it belongs (fig. 2).

There are many possible reasons for such a depression of EPSPs: One is failure of conduction of presynaptic fiber endings. At one time we thought that this might be the mechanism of action of ether. This opinion was based on the observation that, using direct local electrical stimulation of the afferent fibers within the ventral gray matter of the cord, and recording the antidromically conducted discharge from dorsal roots, the excitability of the afferent fibers seemed to decrease during the administration of ether. We argued that as a consequence of the lowered excitability during the action of an anesthetic, the propagation of impulses may stall at points where the safety factor of conduction is small. The terminal arborization of afferent fibers is believed to be such a place of difficult conduction. To test this hypothesis, four kinds of experiments were performed. All four tests turned out negative. First, the time of onset of the EPSP was not delayed by the action of either ether, or thiopental, although its rate of rise and its amplitude were depressed. Second, the presynaptic spike, recorded from

---

* Associate Professor, Department of Physiology and Pharmacology, Duke University, Durham, North Carolina.

Experiments reported here for the first time were supported in part by the Medical Research Council of New Zealand and performed in the Department of Physiology of the University of Otago, and also supported in part by U.S.P.H.S. Grant NB 05330 and performed at Duke University.
Two alternatives remained. Either the release of transmitter substance is prevented by the action of the anesthetic; or, in the presence of the depressant drug the subsynaptic membrane may become less sensitive to the transmitter. The second of these two alternatives seemed more likely, for Thesleff has demonstrated that the depolarizing action of acetylcholine on the endplate of skeletal muscle is reduced by pentobarbital. Frog skeletal muscle may be a rather far-fetched "model" for the mammalian CNS, but recent work on central neurons, from two laboratories, points in the same direction. Crawford and Curtis found that, in the presence of a barbiturate, cortical cells become less responsive to the micro-iontophoretic applications of acetylcholine and D,L-homocysteic acid. Bloom, Costa and Salmoiraghi obtained similar results in the caudate nucleus when they tested the excitability of single neurons with acetylcholine; according to these authors neuronal excitation by glutamate is unchanged by anesthesia.

There is thus increasing evidence that anesthetic drugs interfere with the effect of the

![Image](https://example.com/image.png)

**Fig. 1.** Depression of monosynaptically transmitted excitatory post-synaptic potentials (EPSP's), recorded from a motoneuron in the 7th lumbar spinal segment of a spinal cat; before (left column), during moderate (center), and deep (right column) ether narcosis. Stimulation of nerves of biceps, semitendinosus and gracilis muscles. The weak stimulating pulses were adjusted to give "pure" monosynaptic EPSP's in the unanesthetized state, and were kept at the same strength during ether. "Input" (uppermost three records) monitored from dorsal root-cord junction. Note "spontaneous miniature potentials" ("synaptic noise"), superimposed on the intracellular records of evoked EPSP's, which diminished in amplitude and frequency during anesthesia. (Somjen and Gill)

An extracellular site within the motor nucleus, proved to be stable during administration of ether or thioptalal. Third, post-tetanic potentiation (PTP) was measured. Again, the effectiveness of PTP remained unchanged when the spinal cord was narcotized by these two drugs. Fourth, input and output were constructed as functions of one another before, during and after the administration of ether and thioptalal. These input-output curves shifted along the abscissa, without a change of slope, indicating that the number of synaptic knobs participating in transmission remained unchanged.

From these results we concluded that presynaptic endings, like afferent fiber tracts, conducted action potentials normally in the presence of anesthetics, at least in the spinal cord. Other possible explanations of the depression of the EPSP also appeared to be ruled out by the observations just described. Neither the synthesis, nor the storage of transmitter substance seemed to be affected, for a diminished supply of transmitter should have rendered post-tetanic potentiation less effective.

![Image](https://example.com/image.png)

**Fig. 2.** A. Amplitude of monosynaptic EPSP of a motoneuron of a rat plotted against segmental reflex discharge. Stimulating pulses applied to the fourth lumbar dorsal root, supramaximal for the monosynaptic reflex, recorded from the ventral root of the same segment. This motoneuron has a high threshold and did not produce spike discharges to orthodromic stimulation, only EPSP's. Each point is mean of 3-5 records, at 5-second intervals. Ether administered twice. Oblique crosses: first administration of ether, and partial recovery. Upright crosses: second course of ether, about ½ hour later. The animal was in light pentobarbital anesthesia at the beginning of the experiment. B. Noncorrelation of amplitude of synaptic potential (ordinate) and of resting membrane potential (abscissa) during two courses of ether. Same experiment as 2A. (Somjen and Gill)
transmitter substance on the post-synaptic neuron. It is unlikely that the mechanism of this interference would be the displacement of the transmitter molecule from a binding site by "competition," for ether and barbiturates are dissimilar in chemical structure, yet seem to act in a like manner. More probably, the depressant effect is one of "non-specific stabilization" of the chemically sensitive component of the subsynaptic membrane.²³

There is no reason at present to exclude the possibility that some anesthetics may act both, pre- and postsynaptically. Lating et al.¹⁴ believe that thiamylal acts mainly by reducing the amplitude of the presynaptic spike. With thiopental, we did not observe a depression of the presynaptic spike, but significant quantitative differences of mechanism of action may exist among different drugs, even between different members of the barbiturate family (fig. 7, and last section of this paper). Paton and Spedden ¹¹ have also suggested that failure of transmission may in part be due to decreased output of transmitter from presynaptic terminals. They pointed out that, during anesthesia, the acetylcholine content of the brain is increased. ⁵ It should be remembered however, that transmitter substances may accumulate in an inactive tissue, no matter what causes the depression of activity.

It is easy to see that a depression of synaptic potentials, whatever the mechanism of depression, will cause failure of synaptic transmission. In figure 3 an experiment is shown where progressive lessening of the EPSP led to the disappearance of the spike response of the motoneuron. There is the suggestion (fig. 3) that in addition to the depression of the synaptic potential, there occurred during etherization an elevation of the threshold potential, or trigger level, from which the spike was fired. This kind of effect was seen in many, but not all motoneurons exposed to ether. ⁷ In order to study the effect of anesthetics on the excitability of nerve cells it was necessary to use direct electrical stimulation. In this way the excitatory drive is precisely controlled by the experimenter and is not a dependent variable of the depressant drug.

**Electrical Excitability of Anesthetized Mononeurons**

Individual motoneurons can be stimulated directly by injecting current through a microcapillary electrode lodged in the cell. The same micropipette can be used for recording and for stimulation.⁴,¹¹,²⁵ This method was used in the experiment illustrated in figure 4. During the administration of ether, stimulation either by a constant-intensity ("rectangular"), or by a linearly rising ("triangular") current became less effective. Results from two other cells are plotted in figures 5 and 6. It may be seen that in these experiments "accommodation" to gradually increasing currents was enhanced, and the ability of the cell to respond with sustained repetitive firing was depressed, while the "theobase" (the smallest current that will evoke just one spike) changed little, and sometimes in the wrong direction. When ether was administered repeatedly, the effect was reproducible in the same cell (figs. 5 and 6). In a number of motoneurons however, electrical excitability remained unchanged even in very deep ether narcosis. In one neuron (fig. 5) thiopental seemed inef-
Fig. 4. Direct electrical stimulation of a motoneuron in seventh lumbar segment of a spinal cat, before (first row), during (second row), and after (third row) ether inhalation. On the 1st and 2nd row of records, the upper trace shows the first derivative of the voltage (electrical differentiation), the middle trace the intracellular voltage, the lower trace (partly overlapping the middle trace) the stimulating current. The differential of voltage is omitted in the third row of records. Constant current stimulation of varying intensity was used in the four columns of recording on the left; these are on a common time-base. Linearly rising stimulating current with different slopes on the two columns of records on the right; different time bases, as indicated. Below the oscillograph records are segments from polygraph tracings of the pressure in the femoral artery, and the resting membrane potential of the motoneuron. The three polygraph tracings were taken concurrently with the three rows of oscillograph records. (Experiment not previously published.)

Effective compared to ether. In the cells which were sensitive to ether, the effect became manifest only after several minutes of ether administration, at a time when the segmental reflex was depressed to less than 20–30 per cent of the control amplitude. The effect on the electrical excitability has apparently been equally erratic when other investigators tried other drugs. Sasaki and Otani 28 and Shapovalov 29 described results obtained with pentobarbital which were quite similar to those presented here with ether, but Løying et al.14 found no change of electrical excitability in 4 motoneurons treated with thiamylal. We are currently making efforts to define more precisely the conditions under which the electrical excitability of neurons is affected by anesthetics.

If the effect of depressant drugs on the electrical excitability of neurons is so incaulable, one must ask whether this phenomenon has any importance at all. In the highly artificial situation, where the synaptic drive is an electrically evoked synchronous volley in a collection of nerve fibers, transmission fails mainly because the synaptic potential is depressed; but normally, central neurons do not fire synchronous salvos. Normal function takes place by iterative firing in response to the waxing and waning of asynchronous bombardment by presynaptic impulses; under these conditions the degree of accommodation may become critical. Also the susceptibility to anesthetics of the neurons whose function is most closely related to consciousness, awareness, or attention, may be greater than that of spinal motoneurons.

This leads us to the next question posed, namely the reason for the relative selectivity
of action of drugs on the central nervous system.

Preference Depression of Synapses by Anesthetics

In the absence of precise data, all that we can do at the present time is to discuss the factors that might be involved. These may be divided into two general categories: first, those which are inherent to the organization of nervous tissue; second, those which depend upon the chemical properties of the drug. In the first category are the numbers of synapses arranged in series in a pathway, the efficiency of transmission through each junction, the size of the neurons, and their natural excitability. The possible factors depending upon the nature of the drug are the variations of penetration into, and of uptake within central nervous tissue, and differential binding or adsorption to various types of neurons, or segments of neurons. We shall briefly discuss each of these in turn, insofar as experiments on the spinal cord shed some—even though dim light on the problem.

In a lucid theoretical discussion Bárány pointed out that, other factors being equal, a multisynaptic chain is always more vulnerable than an oligosynaptic pathway. Subsequent experimental work showed, however, that other factors are more important, than the number of synapses interposed, in determining which depressant agent blocks which synapses first.

In the normal, unanesthetized nervous system, synapses of different function vary greatly in the efficiency of transmission. More powerful synapses are recognized by the lack of "subliminal fringe," and the smaller requirement of spatial summation for transmission. By and large, more powerful synapses are more resistant to the depressant action of anesthetics. For example, relay synapses in the "classical" sensory pathways continue to function when spinal reflexes do not.

The size of a neuron would be important if the surface-to-volume ratio could significantly influence the kinetics of uptake or adsorption of the drug, by the cell. In a study of the behavior of motoneurons in the stretch reflex, we found that during ether administration, the smaller of two cells became unresponsive before the larger, in about 35–40 per cent of the trials, even though in the unanesthetized state the smaller neuron was more excitable. This kind of statistical outcome is, unfortunately, undecisive. From elementary considerations of probability, it can be shown that such a proportion of "reversals" of the sequence of recruitment may arise either because smaller cells are more depressed by the anesthetic than larger ones, or simply because the susceptibility of neurons to anesthetic depression is variable, irrespective of size.

Very little is known about the mechanism of
selection of target cells, or synapses, by drugs within central nervous tissue. When administered systemically, many drugs have no or little action on the central nervous system, because their uptake from blood into the brain and spinal cord is sparse. Magnesium ions are an example. Contrary to what is believed by many, systemic administration of magnesium ions has no anesthetic effect. We know this, because with the help of Dr. C. R. Stephen we tried it on ourselves. Figure 7 shows the lack of central depressant effect of MgCl₂ in a cat, in a dose sufficient to cause first, complete paralysis of skeletal muscle, then cardiac standstill.

It can be seen in figure 7 that methohexital, an oxybarbiturate, is a much less powerful depressant of reflex transmission in the spinal cord, than thiopental. This difference was found consistently in four experiments. It would be interesting to know what property of the pharmacological agent is causing these quantitative differences.

Concluding Remarks, and Summary

In addition to a number of poisons, some of which are selective enough to be used as anesthetic drugs, consciousness is easily extinguished by many conditions. Clearly, the neural mechanisms sustaining an alert state of the central nervous system are far less stable than, for example, those driving the respiratory cycle. The reason for these differences between neuronal circuits have, to date, eluded us. In this brief review, it was tacitly assumed that these differences are quantitative rather than qualitative, and that anesthetic agents disrupt the function of the spinal cord in a manner basically similar to their depressant actions on higher brain mechanisms. According to recently published reports, ether and drugs of the barbiturate family interrupt synaptic transmission by depressing excitatory synaptic potentials. This effect is probably caused by a diminished sensitivity of the postsynaptic membrane, to the transmitter substance. It is possible that some drugs also
cause a decrease of the output of transmitter from presynaptic terminals, but definite evidence of a presynaptic effect of anesthetic drugs is as yet lacking. In sufficiently deep ether and pentobarbital anesthesia, the electrical excitability of many, but not all, motoneurons in the spinal cord is also affected; in these cells, the ability to fire repetitively in response to sustained depolarizing currents is lost, and accommodation to gradually increasing currents is enhanced, although the rheobase is elevated only slightly or not at all. It remains to be seen whether this effect, which occurs only irregularly in spinal motoneurons, is important in bringing about the anesthetic state of the brain.

References
G. SOMJEN


DISCUSSION

Dr. Calvin: Were you measuring the transient firing after you initially applied the current?

Dr. Somjen: Yes, I did not wait until the firing frequency settled to a steady level. We used a current of about 0.35 or 0.45 second duration, and counted the number of spikes fired, while the current was on.

Dr. Calvin: The mechanisms causing the transient firing are probably somewhat different than those for the frequency of firing in the steady-state. Have you been able to plot curves of steady-state frequency versus current strength (f-I curves)?

Dr. Somjen: No.

Dr. Calvin: on the triangular ramps of current, when you were plotting the accommodation curves
(firing level vs. latency), these depend upon the membrane potential at which the ramp of current begins. Have you been able to run a complete set of accommodation curves starting at different levels, in both the control and the anesthetic state, to see if there was any change in the actual accommodation.

Dr. Somjen: I agree that there are many more things one could do to a cell, if one had the time. The way these experiments are performed is as follows: One finds a cell, and it seems stable. Recording starts, then administration of ether is begun. If blood pressure changes rapidly, the cell might be lost; one then has to wait another 15 or 20 minutes before starting again. For this reason we cannot spend an hour or more on control records, then another hour during ether, then another hour for the recovery records. We have to do what we can within 15 minutes for each. If we are lucky we can repeat the cycle. By using direct currents of about 0.4 seconds duration we are testing something that is closer to the physiological functioning of the cell than if we were stimulating with very brief pulses of a few milliseconds only. True, in postural movements, neurons may fire for minutes at a time, but movements of a few tenths of a second are physiologically also quite feasible. It was for the same reason, economy of time, that we did not attempt to get complete families of accommodation curves with linearly increasing currents, repeating the testing at different pre-set levels of membrane potential. We are well aware that “accommodation” is dependent upon the prevailing “resting” membrane potential level (Bradley and Somjen: J. Physiol. 156, 75, 1961). This is found empirically, and it also follows from the Hodgkin-Huxley theory of excitation. Although we did not try to control membrane potential by passing a bias current, it is obvious from the figures just shown, that the changes of accommodation during ether were not caused by changes of membrane potential.

Dr. Calvin: What I am concerned about is the effect of cell damage due to the microelectrode. As you have probably noticed, some phasic cells (which fire only transients to a constant stimulus) are phasic only because of cell damage. The best example that I have, is when you withdraw the microelectrode slightly and convert a phasic cell into one which fires continuously to a steady stimulus. Could the phasic behavior of your cells might have been the result of damage?

Dr. Somjen: We would like to compare small cells with large cells, both for changes of electrical excitability during anesthesia, and for the depression of synaptic potentials. The cells I showed were probably not injured. However our sample is badly biased, containing mainly large neurons, for the simple reason that these are easier to find and to hold. We find this inadvertent selection, because our neurons have shorter afterhyperpolarizations, than the average motoneurons. One can find the smaller cells, and hold them too, as long as nothing is done that could cause the slightest movement of the cord. It is possible to stabilize mechanically the blood pressure of an animal, that presumably would reduce the movement of the cord during induction of anesthesia, but that does require rather involved instrumentation.