the absence of coexisting hypercholesterolemia or hypertension.

This possibility is further strengthened by evidence for the role of neuropsychological mechanisms in human ischemic heart disease (*30*). Such mechanisms would of necessity be mediated through the nervous system. Whether they would act directly by affecting the vascular wall through neural transmission or indirectly by elaborating arteriopathic substances (such as angiotensin II) in extravascular sites, can only be answered by future investigation.

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Pentobarbital: Differential Postsynaptic Actions on Sympathetic Ganglion Cells

Abstract. *The frog sympathetic ganglion has been used as a model to elucidate the cellular mechanism of barbiturate anesthesia. Anesthetic concentrations of pentobarbital markedly reduced the fast nicotinic excitatory postsynaptic potential while having no effect on the slow excitatory postsynaptic potential or slow inhibitory postsynaptic potential, even though all three synaptic potentials depend on the presynaptic release of acetylcholine. A similar differential effect was seen for nicotinic and muscarinic responses to exogenously applied agonists, while the depolarizing action of γ-aminobutyric acid (GABA) was enhanced. These results indicate that pentobarbital has remarkably selective actions on the sympathetic ganglion and further indicate that blockade of ganglionic transmission by anesthetic concentrations of pentobarbital can be entirely explained by a postsynaptic action. The present results strengthen the concept that pentobarbital anesthesia results from a postsynaptic blockade of central excitatory synapses which increase sodium conductance coupled with a postsynaptic enhancement of GABA-mediated synaptic inhibition.*

It is well documented that barbiturates have a remarkably selective action on synaptic transmission, and it is generally agreed that alterations in synaptic function play a crucial role in producing general anesthesia. However, the exact site at which these drugs act remains controversial. On the one hand there is evidence that barbiturates have presynaptic effects which could lead to the blockade of transmitter release (*1, 2*), while on the other hand there is considerable evidence that barbiturates act postsynaptically to block excitatory transmitter action (*3–7*). Moreover, the preservation or augmentation of synaptic inhibition in the presence of barbiturates both in the vertebrate central nervous system (*8*) and invertebrate systems (*9*) suggests that a block of inhibitory transmitter release is not occurring. This differential action of barbiturates also indicates a striking selectivity of barbiturates for certain types of synapses. The sympathetic ganglion is a particularly useful preparation to examine the selectivity of barbiturate action, since a variety of synaptic potentials can be recorded (*10, 11*). In addition, insight can be gained into the relative importance of pre- and postsynaptic sites of action.

Changes in membrane potential of frog (*Rana catesbeiana*) paravertebral sympathetic neurons were recorded by the sucrose gap technique from the ninth or tenth postganglionic branch (*12*). Initial studies confirmed that transmission through the frog sympathetic ganglion was much more sensitive to barbiturates than was axonal conduction (*13*). Thus a 50 percent block of synaptic transmission occurred at a concentration of 100 μM pentobarbital, while a 50 percent block of axonal conduction required approximately a 20-fold increase in concentration. Examination of the relative sensitivity of the various synaptic potentials indicated an additional highly selective action. Figure 1A shows that pentobarbital severely depresses the fast excitatory postsynaptic potential (EPSP) but has no effect on the slow inhibitory postsynaptic potential (IPSP) or slow EPSP. A 50 percent reduction in the fast EPSP occurred at a concentration of 100 μM ($N = 8$). To reduce the slow potentials to a similar extent required increasing the concentration approximately tenfold. This differential sensitivity, although less pronounced, was seen with a number of other general anesthetics including ketamine, chloral hydrate, chloralase, ether, and halothane. The convulsant barbiturate 5-(2-cyclohexylideneethyl)-5-ethyl barbituric acid also had a selective action. These results complement other research on the effect of anesthetics on ganglionic discharges (*14*).

A comparison of the action of pentobarbital was also made on the depolarization produced by γ-aminobutyric acid (GABA), which in mammalian ganglia results from an increase in chloride conductance (*15*); β-alanine, which weakly mimics GABA in sympathetic ganglia (*16*); and carbachol. Whereas pentobarbital (100 μM) reduced the amplitude of the carbachol response an average of 80 percent ($N = 6$), the amplitude of the GABA and β-alanine responses was actually increased and prolonged (Fig. 1B). This effect on GABA responses is consistent with observations on central neurons that GABA-mediated synaptic inhibition (*8*) and the action of exogenously applied GABA (*4, 7*) are prolonged by

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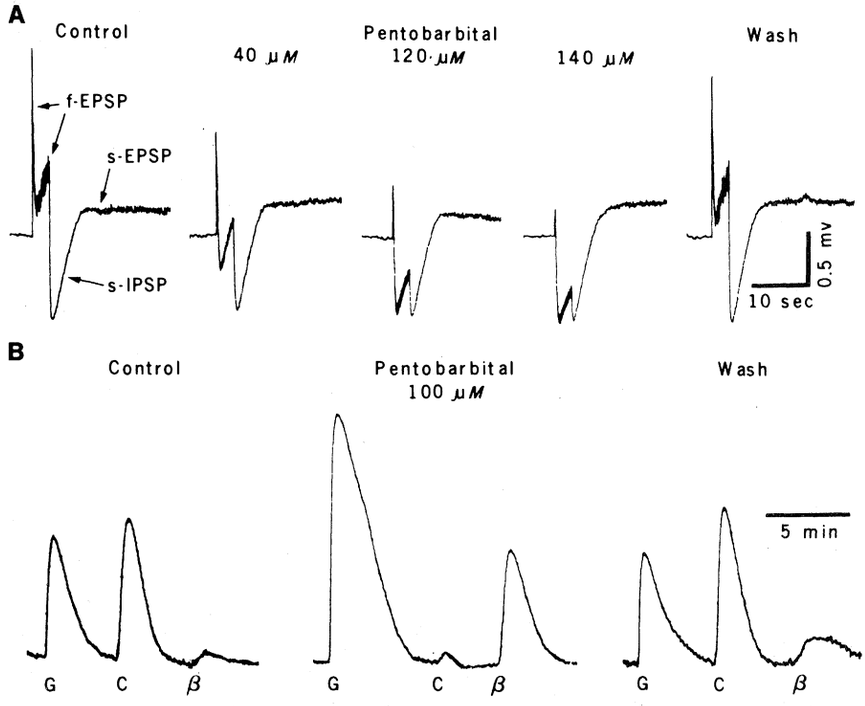

Fig. 1. Differential postsynaptic effects of pentobarbital on frog sympathetic ganglion. (A) Increasing concentrations of pentobarbital markedly depress the fast EPSP (*f-EPSP*) but have no effect on the slow EPSP (*s-EPSP*) or slow IPSP (*s-IPSP*), which were elicited by a stimulus frequency of 60 hertz. (B) Brief applications of carbachol (*C*), GABA (*G*), and β-alanine (*β*) depolarize the ganglion. Pentobarbital (100 μ*M*) blocks the carbachol response but augments the GABA and β-alanine responses. Carbachol (20 μ*M*) was applied for 15 seconds, GABA (40 μ*M*) for 10 seconds, and β-alanine (120 μ*M*) for 30 seconds. The voltage calibration in (B) is the same as in (A).

pentobarbital (*17*). This same concentration of pentobarbital had little effect on the muscarinic depolarization of ganglion cells by methacholine.

These results show that of a variety of ganglionic responses only the fast nicotinic EPSP is depressed by anesthetic concentrations of pentobarbital. The fast EPSP is generated by an increase in sodium and potassium conductance (*11*). Although the electrogenic mechanisms of the slow potentials are not yet clearly established, it is at least evident that they are not based on an increase in membrane conductance (*10, 11, 18*). The fact that excitatory responses to other neurotransmitters, such as glutamate, which also increase sodium conductance, are blocked by barbiturates (*4, 6, 7*) suggests that the ionic channel opened by these excitatory transmitters is uniquely sensitive to barbiturates and other general anesthetics (*5, 6*).

Since anesthetic concentrations of pentobarbital have no effect on the slow IPSP and slow EPSP, which are both dependent on the presynaptic release of acetylcholine, the depression of the fast EPSP and ganglionic transmission would appear to be entirely a postsynaptic event (*19*). This conclusion is supported by the finding that the sensitivity of the carbachol depolarization is as great or greater than the fast EPSP to pentobarbital. The insensitivity of the slow IPSP is particularly noteworthy since this potential is generated by small, unmyelinated, preganglionic C fibers and, in addition, is thought to involve the muscarinic activation of an interneuron (*10*). It has been suggested that the sensitivity of central synapses to anesthetics might result from impulse blockade in the small presynaptic terminals (*3*). However, the present finding with the slow IPSP would tend to minimize the importance of presynaptic fiber size and also suggests that the addition of synapses in a pathway does not necessarily increase its sensitivity to barbiturates. Rather, it is the type of synapse in the pathway which determines its sensitivity to barbiturates and other anesthetics.

In summary, the present results demonstrate that anesthetic concentrations (100 to 120 μ*M*) of pentobarbital (i) have a strikingly selective depressant action on the fast nicotinic EPSP in sympathetic ganglion cells, (ii) depress ganglionic transmission solely by this postsynaptic action, and (iii) augment the action of GABA. These results emphasize the remarkable differential and selective effect that pentobarbital has on synaptic and drug-induced potentials. A comparison of the present results with those obtained at central synapses suggests that pentobarbital anesthesia results from a postsynaptic blockade of excitatory synapses which elicit an increase in sodium conductance, coupled with a postsynaptic enhancement of GABA-mediated synaptic inhibition.

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