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Mechanisms of Barbiturate Protection

NEUROLOGIC SEQUELAE following an episode of cerebral hypoxia present grave problems for the individual patient, and are responsible for major socioeconomic problems. The number of stroke patients is large, and with continuing improvements in supportive medical care, the percentage of survivors is increasing, creating a growing demand for extended nursing care. Other medical advancements have added to the problem. New breakthroughs have occurred in cardiopulmonary resuscitation during the last decades, but of survivors, 20 per cent sustain severe brain damage.[1]

The ground has therefore been ripe for methods that could protect the brain from hypoxic damage, or possibly ameliorate the damage once caused. Unfortunately, we still do not understand the basic nature of hypoxic damage to neurons, or even whether the mechanism is the same in different kinds of hypoxia. Impairment of mitochondrial ATP production has been suggested, but this can be normal even in the presence of severe neurologic deficits. Because energy utilization is usually reduced in such circumstances, it is more likely that the primary insult takes place in a function requiring ATP.[2] Partly due to our lack of basic knowledge, a host of therapeutic modalities have been suggested, many of them empirical, without a scientifically based mode of action. It is, therefore, not surprising that few of these seem to have had any effect upon the eventual outcome for the patient. At the moment the only theoretically established therapeutic principle is to improve the ratio of oxygen supply to oxygen demand.

More than 30 years ago, barbiturates were found to reduce the rate of cerebral oxygen consumption.[3] Arnfred and Secher, in 1962,[4] found that barbiturates prolonged the survival of hypoxic mice, and Smith *et al.*[5] later demonstrated protection by barbiturates following occlusion of a middle cerebral artery in dogs. In both these models, hypoxemia and incomplete regional ischemia, protection can be explained by reduction in the oxygen demand in a situation where the oxygen delivery is greatly reduced, but not absent. Rockoff *et al.*[6] have demonstrated also the potential effectiveness of barbiturates in reducing an increased intracranial pressure. Protection in regional ischemia might be explained by this effect, or by the "reverse steal" phenomenon, where vasoconstriction by barbiturates in nonischemic areas of the brain increases perfusion pressure in ischemic areas. The latter can only occur secondary to a decrease in ICP or when there is a significant vascular resistance in series with those vessels influenced by barbiturates or ischemia.

In addition to protection in hypoxemia and incomplete ischemia, Goldstein *et al.*[7] reported protection with barbiturates when the oxygen supply was completely cut off (global anoxia), and Bleyaert *et al.*[8] reported amelioration when barbiturates were given after such an anoxic event. These results cannot be readily explained by any of the above-described mechanisms and, although the validity of these studies has been challenged, they have stimulated a search for other possible mechanisms. In an interesting paper in the present issue, Smith *et al.*[9] examined the hypothesis that barbiturates protect (or ameliorate) because they can neutralize or scavenge free radicals that would otherwise damage the neurons during or following a hypoxic event. This hypothesis was originally advanced by Demopoulos *et al.*[10]

Most molecules have paired electrons in their electron orbitals. The two electrons have opposite spins and thus cancel each other's magnetic fields. This gives a favorable low-energy state. A free radical is a molecule with an unpaired electron in an outer orbital and, hence, it is in a high-energy state and

extremely reactive. Many compounds can be converted into free radicals by energy transfer, such as with irradiation by gamma or x-rays or thermal homolysis of bonds, or by chemical agents known as initiators.

Key biomolecules within cell membranes and in other macromolecular aggregates are highly susceptible to radical reactions, which will change their physical–chemical properties and shapes considerably. Abnormal uncontrolled free radical reactions have therefore been suggested to be of crucial importance in a variety of disease states such as arthritis, alcoholic or halothane hepatic disorders, radiation damage, and oxygen toxicity. Oxygen is of general importance in free radical abnormalities. Molecular oxygen is capable of being a diradical, ȯ-ȯ. Two of the electrons are not always shared between the two oxygen atoms, and this makes it possible for oxygen to be an initiator of free radical reactions.[11] Since oxygen is much more soluble in nonpolar than in polar media, it will be most concentrated in the midzone of cell membranes. There, unsaturated fatty acids are likely to be attacked in lipid peroxidation, often a chain reaction, and this can change the entire membrane structure.

Free radical reactions do not occur only in pathologic states, but are part of normal cellular metabolism. Because of the potential for severe damage, these reactions must be well controlled. This can occur by quenching, a chemical reaction where the free radicals are scavenged. Superoxide, O_2^-, is a free radical that is normally present in minute amounts in respiring cells. It might be responsible for oxygen toxicity, but can be catalytically scavenged by the enzyme superoxide dismutase.

$$O_2^- + O_2^- + 2\,H^+ \rightarrow H_2O_2 + O_2$$

This enzyme is thus essential for the survival of aerobic cells, but is apparently missing in obligate anaerobic cells.[12] Free radical control can also be imposed by the membrane structure. If free radical intermediates in a normal reaction chain are very short-lived and tightly bound, chemically and sterically, there is little chance of abnormal reactions disrupting the cell structures. This is the case in the electron transport chain, where naturally occurring radical intermediates in coenzyme Q and other sites very easily can donate their electrons further down the chain; thus, the mitochondria stay intact. In hypoxia there is a shortage of the normal electron acceptor at the end of the chain; this could result in an increase in the level of free radicals within the chain and initiate reactions which disrupt mitochondrial membranes.[13]

Following occlusion of a middle cerebral artery in cats, Flamm *et al.*[14] found indications of increased free radical production which could be completely blocked by the administration of methohexital. *In-vitro* studies by the same investigators also indicated that methohexital could scavenge at least some free radicals.[15] It was thus postulated that free radical-associated abnormalities were important in hypoxic damage, and that barbiturates were protecting as free radical scavengers. Their *in-vivo* results can be interpreted differently. With occlusion of the middle cerebral artery, blood flow in the ischemic area is reduced to 30–40 per cent of control. If the oxygen consumption in the same area is halved by barbiturates, there would be no severe hypoxia, and thus no evidence of free radical damage. There would be no need for a scavenger.

Since cerebral protection has been reported to occur with a variety of barbiturates, all should be effective scavengers if this is the protective mechanism. This is not the case, according to Smith *et al.*[9] They studied the quenching of free radical reactions *in vitro* using four different barbiturates, all known to afford cerebral protection. Where thiopental effectively inhibited free radical-induced damage, methohexital afforded little and pentobarbital and phenobarbital no inhibitory effect. The study does leave some questions unanswered. The free radical production was initiated by iron and ascorbate; thus, it cannot be ruled out that thiopental was acting by simply chelating the iron. The lack of effectiveness of methohexital is also contrary to the *in-vitro* results of Demopoulos *et al.*[15] It is known that different radicals may require different scavengers. It is thus possible that the radicals produced in the study of Smith *et al.* are not the ones responsible for hypoxic damage. This can be resolved only by studying cerebral hypoxia *in vivo*. It is thus most interesting that Flamm *et al.*[13] seem recently to have found a difference between barbiturates *in vivo* also. In this study they found strong indications of free radical production during pentobarbital anesthesia and occlusion of the middle cerebral artery, in contrast to their previous methohexital results.[14] In support of the negative findings of Smith *et al.*, we reported[16] that cerebral protection correlated well with depth of anesthesia, but not with brain concentrations of barbiturates. The latter should be the case if quenching of free radical reactions were an important protective mechanism. On balance, therefore, it appears unlikely that barbiturates protect because they scavenge free radicals.

The studies by Flamm *et al.*[13,14] nevertheless represent an important step forward in the approach to uncovering methods that might protect the brain

from hypoxia. They focused on possible molecular mechanisms of damage and logically tested these both *in vitro* and *in vivo*. By contrast, the approach of screening a large number of drugs in an attempt to find cerebral protection without a sound hypothesis for the mechanisms of damage and protection is less likely to give lasting results. Ultimately, only when we know the molecular basis for hypoxic damage can we systematically investigate protective and possibly even ameliorating therapeutic modalities.

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