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A Comfortable Hypothesis Reevaluated

Cerebral Metabolic Depression and Brain Protection during Ischemia

For decades, anesthesiologists have been interested in cerebral hypoxia and ischemia and in methods of protecting the brain in the face of such conditions. We have also long taken a conceptual approach to cerebral protection similar to one that has proven useful in cardiac physiology, *i.e.*, control of supply and demand. We have believed that we could protect the brain by either increasing nutrient and oxygen supply, or, more importantly, by reducing metabolic rate. The value of increasing supply is not arguable. However, agents or interventions that reduce cerebral metabolic rate (CMR) are also viewed as "protective," particularly if this decrease in CMR is accompanied by EEG suppression.

Unfortunately, although this concept may be intuitively satisfying, the report by Sano *et al.* in this issue of ANESTHESIOLOGY suggests that it maybe incomplete or incorrect.[1] The authors subjected rats to a standardized forebrain ischemic insult. Animals were anesthetized with 1.3 MAC halothane or isoflurane or with halothane combined with mild hypothermia (head temperature = 35° C!). Both of the normothermic groups showed histologic evidence of severe brain damage, indicating that isoflurane did not offer any protective effects. However, damage was dramatically reduced by hypothermia. Sano *et al.* did not measure CMR, nor did they record the EEG, but there is ample evidence that isoflurane in the doses used produces 1) burst suppression on the EEG and 2) values for CMR of glucose that are 30–50% less than those seen with halothane. Furthermore, CMR should be reduced at 35° C by only 15–20% (*i.e.*, substantially less than is achieved with isoflurane).[2] It is thus clear that the degree of neuropathologic injury in the three groups did not correlate with the magnitude of metabolic (or EEG) depression.

The idea that hypothermia and anesthetics differ in their protective effects is not new. In 1978, Michenfelder argued that barbiturates acted by reducing the fraction of CMR that is linked to synaptic activity.[3] He concluded that barbiturates would offer little protection if ischemia had rendered the EEG isoelectric. Because hypothermia affects all biochemical reactions, it should be protective even in the face of marked EEG suppression. However, although Michenfelder carefully avoided concluding that protection is directly related to CMR *per se*, we believe that most anesthesiologists have interpreted his words as supporting the "metabolic depression protects" hypothesis. The contradictory data by Sano *et al.* now adds to a growing body of work that indicates a modification of this idea is needed. There are two general reasons. First, the protective efficacy of different anesthetics does not parallel their ability to suppress the EEG or depress CMR, and second, the protective value of hypothermia is not proportional to CMR depression, nor is it clearly related to the accumulation of metabolic byproducts (which should be influenced by CMR).

Anesthetics

Barbiturates have little value in severe global ischemia but they can reduce infarct volume in focal ischemia. Certain information led many to conclude that isoflurane might share these protective properties. Isoflurane produces EEG and CMR changes similar to the those produced by barbiturates and can retard the accumulation of lactate and slow ATP depletion during mild ischemia. It seems to reduce the incidence of EEG changes in the minutes after carotid occlusion (as compared with halothane) and may reduce the CBF at which these changes occur.[4] A recent study in our laboratory also shows that 0.75 MAC isoflurane significantly prolongs the time to terminal membrane depolarization during a cardiac arrest in rats (77 ± 7 s for halothane and 102 ± 19 s for isoflurane, mean ± standard deviation).* However, repeated studies examining neurologic and/or histopathologic *outcome* after global and focal ischemia have failed to demonstrate protection by isoflurane.[1,5–7] This failure to protect during focal cerebral ischemia is not due to an unfavorable redistribution of CBF produced by isoflurane† and hence remains "unexplained."

Baughman and colleagues have shown some isoflurane-related protection in a model of *modest* global ischemia/hypoxia, at least relative to control animals receiving only nitrous oxide (which is not an anesthetic in the rat).[8] However, if one combines the results of three studies done by these authors using the same model,[8–10] it appears (our interpretation) that the magnitude of protection is not

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* Verhaegen M, Todd M, Warner D: A comparison of cerebral ischemic flow thresholds during halothane/N_2O and isoflurane/N_2O anesthesia in rats. ANESTHESIOLOGY 1992, in press.

† Warner D, Hansen T, Vust L, Todd M: Distribution of cerebral blood flow during deep isoflurane vs. pentobarbital anesthesia in rats with middle cerebral artery occlusion. J Neurosurg Anesth 1:219–226, 1989

dose-related for a given agent, nor does it correlate well with preischemic CMR, at least when the high CMR values in the nitrous oxide–only animals are excluded. For example, rats given low-dose methohexital (CMR of oxygen = 9.1 ml · 100 g^{-1} · min^{-1}, active EEG) and subjected to 30 min of "moderate ischemia" (unilateral carotid occlusion, mean arterial pressure = 30 min, FI_{O_2} = 0.30) had identical functional and histopathologic outcomes as did rats given high-dose methohexital (CMR of oxygen = 4.3, burst-suppressed EEG).[10],‡ Similarly, outcome with halothane anesthesia was no different than with isoflurane, despite metabolic differences.[8] In further support of our hypothesis are two anesthetics (dizocilpine and dexmedetomidine) that have protective properties[12,13] but little or no influence on CMR,[14,15] and at least one anesthetic (propofol) that can slow the EEG and reduce CMR but which seems to have little protective efficacy at least against focal ischemia.§,¶ Finally, while halothane and isoflurane resulted in different times to terminal cortical depolarization (see above), the times to EEG isoelectricity are identical (8–9 s).* If the "protective" effects of anesthetics are related only to EEG-linked CMR, why should the subsequent times to depolarization (in the face of a flat EEG) be so different?

Hypothermia

Beginning in the early 1980s, a number of simple rodent models of cerebral ischemia were developed (such as that used by Sano *et al.*[1]). Unfortunately, one problem with these models was the variability in histologic damage that was seen even when a standardized insult was produced in genetically similar animals. A large portion of this variability is now attributed to hypothermia: it was demonstrated in 1987 that during ischemia, brain temperature rapidly decreases unless actively maintained.[16] Several studies have now demonstrated that changes in brain temperature of as little as 2–4° C are associated with substantial effects on histologic damage.[17,18]

It has long been assumed that hypothermic protection is metabolically mediated: hypothermia leads to reduced demand, which results in increased ischemic tolerance. Because CMR decreases in a log-linear fashion with decreasing temperature,[2,19] one would expect that progressively greater reductions in body temperature would be associated with a parallel decrease in ischemic damage. However, the studies noted above have shown that a sigmoid and not a log-linear relationship is observed when brain temperature is correlated with histologic damage, at least when we are dealing with mild hypothermia. When Busto *et al.* reduced brain temperature in rats from 39 to 36° C, the number of dead neurons in the striatum produced by an ischemic insult was decreased by 25%.[16] With an additional 2° C decrease (to 34° C), the number of dead neurons was near zero. This is consistent with the almost total protection seen by Sano *et al.* at 35° C.[1] Similar observations have been made at 33° C during temporary focal ischemia.[18] Apparently paradoxical results can also be found on examination of the changes in high-energy phosphates and lactates during ischemia. Busto *et al.* subjected rats to 20 min of forebrain ischemia at brain temperatures of 36, 33, and 30°C. While a dramatic protective effect (by histology) was seen at 33° C, energy charge, ATP, and lactate concentrations were no different than those seen in animals at 36° C.[16] In 1989, Natale and D'Alecy subjected dogs to 10 min of ventricular fibrillation at measured brain temperatures of either 37–39 or 33–34°C.[20] The hypothermic dogs all survived for 24 h postinsult, whereas all normothermic animals died. However, when brain tissue lactate concentrations were examined (in parallel groups), no differences were seen either during or after ischemia. Since a slowing of a metabolic demand should also slow the depletion of ATP and the accumulation of lactate, such findings are difficult to reconcile with a "metabolic" explanation for hypothermic protection.

Alternative Hypotheses

If the protective effect of anesthetics and hypothermia cannot be explained by metabolic depression, what alternative hypothesis are available? It is known that ischemia triggers a cascade of biochemical events. In particular, there is a massive release of multiple neurotransmitters, one of which is glutamate, the principal excitatory transmitter in the brain.[21,22] The excitatory properties of glutamate are believed to result in postsynaptic depolarization and calcium entry. This influx of calcium triggers the release of free fatty acids (which results in the synthesis of various membrane-active compounds), the production of both oxygen and hydroxyl free radicals, and the uncoupling of mitochondrial oxidative metabolism. These changes may persist into the postischemic period, leading to the belief that calcium entry is the mediator of neuronal death.[23] The high concentrations of extracellular glutamate seen during ischemia rapidly return to normal—but either the transient increase (or some other event) may lead to an enhanced sensitivity of glutamate receptors to activation, with the result being a continued calcium influx. This is, of course, only a partial list of the events,

‡ Note that contrary to popular opinion, barbiturate protection has never been firmly linked to CMR depression. For example, Michenfelder and Sundt found dramatic protection in primates with quite low pentobarbital doses.[11]

§ Gelb A: Personal communication.

¶ Ridenour T, Warner D, Todd M, Gionet T: Comparative effects of propofol and halothane on outcome from temporary middle cerebral artery occlusion in the rat. unpublished data

which includes such changes such as altered protein synthesis and changes in gene expression.[24–26]

In very simplified terms, ischemic injury can be temporally divided in to three phases, each one of which can be targeted by protective therapies. The first is the period between the initial reduction in CBF and complete energy failure, which is signaled by membrane depolarization. Anesthetics and hypothermia *can* reduce metabolic demand, can slow the depletion of high energy phosphates, and can delay the time to depolarization. If ischemia is mild, anesthetics may provide some protection by the simple act of "buying time"—but it appears that all of the commonly used anesthetics seem to protect to an approximately equivalent degree. However, as ischemic conditions worsen, the amount of "time bought" becomes irrelevantly short (*i.e.*, 1–2 min), and the degree of protection that can be achieved by targeting this interval is probably of minimal relevance.

Once depolarization occurs and the biochemical cascade noted above has been triggered, we must look to something other than metabolic depression. Two basic approaches can be taken: prevent the release or synthesis of various detrimental compounds, or block the action of these compounds at their sites of action. It is now known that mild hypothermia can block the release of glutamate that occurs with ischemia.[27] We do not yet know how anesthetics influence this event. The deleterious effects of glutamate (and other excitatory transmitters) can be attenuated by blocking the appropriate receptors.[28] For example, drugs like dizocilpine and NBQX block the action of glutamate at two of its receptor sites, the N-methyl-d-aspartate receptor and the quisqualate or AMPA receptor respectively. Other anesthetics, such as dexmedetomidine may protect by augmenting inhibitory transmission. Drugs like isoflurane and barbiturates are incompletely evaluated with respect to glutamate antagonism, but such effects, if present, are modest compared to those elicited by receptor specific antagonists.

When reperfusion of ischemic tissue begins, a third series of events takes place—and far less is known about these events than about those that occur during the other two phases. One important change is the enhanced release of various free radicals caused by the reintroduction of oxygen into previously ischemic tissue. Whether anesthetics can play any role during this period remains unclear, although most anesthetics are relatively poor direct free radical scavengers. A recent study does indicate that postischemic hypermetabolism does not occur[29] (at least in the absence of seizures), and thus it again appears unlikely that an anesthetic will have any metabolically mediated benefit.

In summary, we believe that the available evidence demonstrates that anesthesia *per se* probably does have some protective properties. Apparently, metabolic depression also modestly prolongs the time to neuronal depolarization. However, this delay is only on the order of 1–3 min, at least when ischemia is sufficiently severe as to produced serious tissue damage. Whether anesthetics can alter the biochemical cascade triggered by depolarization (which can be clearly altered with mild hypothermia) or the consequences of reperfusion is far less clear. However, it is clear that the time is come for anesthesiologists to change their approach to protective therapy. In a recent editorial in ANESTHESIOLOGY, we noted that "Our mechanistic concepts of brain injury and protection govern the way we search for answers. If our concepts are wrong, we may look in the wrong places for those answers.[30]" We believe that our concepts are at least partly wrong, and that we may have been looking in the wrong places for too long. The metabolic depressant effects of anesthetics (and probably mild hypothermia) seem to contribute little to their practical protective value.

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