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Anesthetic Neuroprotection? It's Complicated

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Anesthetics possess numerous pharmacologic properties consistent with increased tolerance of brain to an ischemic insult. Despite investigation for over half a century,¹ and robust demonstration of such benefit in laboratory animals,² there is no solid evidence that anesthetic neuroprotection is present in humans.³ The article by Archer et al.⁴ in this issue of *ANESTHESIOLOGY* provides considerable insight into this apparent paradox.

It once seemed so straight forward. The brain consumes ATP at an incredible rate and holds little stores of this critical metabolite. Hence, continuous delivery of oxygen and glucose are essential to maintain ATP synthesis, neural function, and cellular integrity. If the tissue demand for these substrates is suppressed by an anesthetic (which most anesthetics readily produce), then the duration brain can survive in low-flow or no-flow states should be increased substantially. Hence, the world of pharmacologic neuroprotection was largely held within the perioperative environment for several decades. Anesthesiologists and surgeons were at the forefront of neuroprotection research.

In the late 1980s, problems arose for the metabolic suppression hypothesis. Non-anesthetic drugs that had little or no effect on metabolic rate were found highly neuroprotective in the laboratory. Evidence rapidly grew in support of protective benefits from mild hypothermia, which again induced little change in metabolic rate. It was becoming clear that other critical mechanisms were in play. And later, it became evident that exposure of brain to a mild stressor stimulus, either before (pre-conditioning) or after (post-conditioning) a severe ischemic insult set in play a biomolecular cascade that improved ischemic outcome. It is now known that anesthetics can also serve as effective conditioning stimuli, again independent of effects on metabolic rate during the ischemic insult. At the same time, a series of failures in detecting anesthetic neuroprotection in clinical trials accumulated, dashing almost all hope for such intervention. Hence, there was a pivot of investigation away from neuroprotection in the perioperative environment towards development of non-sedative drugs relevant to the large number of patients who sustain out-of-hospital stroke.

While the above logic sequence seems reasonable, is it all correct? The fact remains that after trials of scores of drugs in human stroke, other than tissue plasminogen activator, there is no pharmacologic intervention proven efficacious for any form of stroke in humans. This body of failure has led to serious questions regarding the pathway from bench to bedside.

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Most such focus has been on the preclinical side of efficacy analysis. While major flaws in clinical trial designs must also be considered, lessons from the preclinical stroke research community are highly relevant to study of anesthetics in the perioperative environment. Our method of translating from bench to operating table should also be reconsidered.

This is where the work of Archer et al. becomes important.⁴ Using a robust search strategy, 80 laboratory investigations were identified that employed the intraluminal filament middle cerebral artery occlusion (fMCAO) model⁵ to investigate anesthetic neuroprotection in rodents. Although this focal ischemia model has been criticized for near-instantaneous flow restoration compared to gradual restoration of flow occurring with endogenous or pharmacologic thrombolysis,⁶ the model may be relevant to anesthetic neuroprotection. Rapid flow restoration occurs with numerous perioperative events (e.g., temporary vessel occlusion during cerebral aneurysm and carotid surgery). Further, the model is widely employed allowing this search strategy to capture a large body of research and the model has been the workhorse for study of non-anesthetic neuroprotective drugs. Hence, parallels from that body of literature can be also drawn. The results of the Archer et al.⁴ analysis were surprising.

A unique feature of this work was use of an established systematic scoring system to grade quality of the studies. Strengths of the body of research were use of physiologic monitoring, randomization, and blinded outcome assessment, and publication in peer-reviewed literature. A major weakness was lack of pilot data and sample size calculation. This is important because the number of animals studied can define the robustness of the experiment to definitively capture the effect size of the treatment. If an insufficient number of animals is studied, the experiment could either over- or underestimate how effective the drug is. Clinical investigators need to know the true effect size to decide whether to do a trial and if so, how many patients should be enrolled to detect it. Archer et al.⁴ found that across anesthetics the *reported* effect size (i.e., improvement in histologic and neurologic outcome) averaged 30% in the higher quality studies. But, the potential range of *true* effect sizes was calculated to be 3–58%. In other words, use of small sample sizes in controlled laboratory investigations could erroneously produce evidence of an effect size that had no chance of being detected in a heterogeneous human surgical population. Only with study of a large number of animals can the true effect size be defined. This exceeds the capacity of any one laboratory. Archer et al.⁴ point out that this same problem is paralleled in the study of non-anesthetic stroke drugs. Recognition of this limitation has led the stroke community to advocate use of multi-institutional pre-clinical trials before any drug is advanced to human study.⁷ Indeed, such an effort has now been achieved,⁸ and can serve as a model for how anesthetics should be vetted before human study is initiated.

Another interesting finding was lack of anesthetic neuroprotection in females. This is not novel in the world of neuroprotection research investigating non-anesthetic drugs. Based on lines of evidence from study of neuroprotective interventions, stroke drug development advisory panels have long advocated preclinical testing in females and males before advancing a compound to clinical trials.^{9–11} The National Institutes of Health now requires sex to be accounted for as a biological variable in all preclinical studies conducted in animals and even cell lines.¹² It is noteworthy, however, that Archer et al.⁴ conclude sex to

be an important determinant of anesthetic neuroprotection on the basis of the only study designed to specifically investigate this.¹³ That study was markedly limited in experimental design and clinical relevance, most notably use of only a 24 hour post-stroke recovery interval, which is now widely accepted to be insufficient to measure final stroke outcome.¹⁴ Regardless, the fact that 78 of 80 studies reviewed by Archer et al.⁴ were conducted on adult male rodents is sufficient evidence to conclude that effort must be made to determine the role of sex in the question of anesthetic neuroprotection.

A final highlight from the review was the finding that anesthetic neuroprotection was absent in aged animals and those with comorbidities (e.g., hypertension, diabetes). Again, the number of such studies was few preventing a meaningful conclusion to this consideration. But, what was enticing was that Archer et al.⁴ also compiled mechanisms of action for anesthetic neuroprotection amongst the studies evaluated. When aged animals and those with co-morbidities were segregated, a pattern of anesthetic-mediated suppression of pro-survival pathways was present. Notably, all of these studies were conducted in post-conditioning experiments. Whether anesthetic post-conditioning evolves to a therapy in humans, this finding could have implications for aged patients subjected to anesthesia *after* ischemic stroke. If the aged post-stroke brain is vulnerable to anesthesia, the at-risk interval should be mechanistically determined in concert with outcome analysis. Further, for sex, aging, and co-morbidities it would be imperative to assess significance of these factors in a diverse array of experiments to ensure that neuroprotective findings are not species or model specific.

The work of Archer et al.⁴ is a report card on the research community's efforts to understand anesthetic neuroprotection and the finding is that such work remains insufficient. To a large extent, study of anesthetic neuroprotection has become a dormant field given the litany of failed human studies investigating this potential. But, patients still require anesthesia and still suffer ischemic insults in that context. This has become even more poignant with convergent recent evidence that endovascular thrombectomy is efficacious for out-of-hospital acute ischemic stroke;¹⁵ many patients receive anesthetics for this procedure. Archer et al.⁴ have defined weak links in our knowledge and offer potentially fruitful areas of investigation to better understand which patients under which conditions might be suitable for further investigation of anesthetic efficacy or adverse effects.

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