Is Gene Therapy in Our Future?

IN this issue of Anesthesiology, Tao and Johns\(^1\) show that the protein PSD-95/SAP90 is required for normal function of the N-methyl-D-aspartate (NMDA) receptor *in vitro* and that normal NMDA receptor function plays a role in determining isoflurane minimum alveolar concentration (MAC). These findings are not completely surprising given that earlier studies cited by the authors have shown that PSD-95/SAP90 is important in transduction of the NMDA receptor\(^2\)–\(^4\) and that blockade of the NMDA receptor reduces isoflurane MAC.\(^5\)\(^,\)\(^6\) What is novel about this study is the use of “genetic” techniques in the form of antisense oligodeoxyribonucleotides (ASODs) to reduce translation of PSD-95/SAP90 messenger RNA into functional protein. Although all anesthesiologists are familiar with the use of receptor agonists and antagonists as research tools, the use of genetic techniques in pharmacologic research is beyond the experience of most clinicians. Therefore, the reader who lacks familiarity with genetic techniques would do well to read the paper by Tao and Johns carefully because it provides an excellent description of rationale for use of antisense oligodeoxyribonucleotides and an excellent example of the appropriate way to use them as research tools.

Although genetic techniques are powerful research tools that are revolutionizing study of the medical sciences, they are fraught with some of the same limitations as are more traditional pharmacologic techniques. For example, the authors imply that the decrease in isoflurane MAC caused by knockdown of PSD-95/SAP90 indicates that PSD-95/SAP90 may be a site of volatile anesthetic action. However, this conclusion seems premature. For example, MAC also is decreased by intrathecal local anesthetics and opioids, but this cannot be construed to indicate that Na\(^+\) channels and opioid receptors are sites of volatile anesthetic action. Rather, all of these facts are consistent with a more simplified view that volatile anesthetic MAC depends on normal processing of sensory information. Therefore, diminishing painful afferent sensation by decreasing the amount of PSD-95/SAP90 present may reduce MAC but may not tell us a great deal about the specific site of volatile anesthetic action.

Tao and Johns also imply that there eventually may be clinical applications for their findings. Clearly, their study was not intended to develop clinical applications of antisense oligodeoxyribonucleotides; however, their suggestion of eventual clinical use serves as an invitation to use their study as a framework to consider the future role of genetic techniques in clinical anesthesia.

The pharmaceutical industry spends hundreds of millions of dollars each year to develop genetic approaches to disease treatment. Because they hope to profit from their investment, the next decade will bring significant pressure to use new classes of biopharmaceuticals that target gene expression. Most of the initial applications of this “new pharmacology” will be for treatment of cancer or diseases that result from a single mutation, such as cystic fibrosis. However, Tao and Johns show that there may be a role for such techniques in anesthesia as well. This being the case, several questions come to mind, the most important of which is, why bother?

This is not to imply that reducing pain transmission *via* interference with the NMDA system is not a potentially useful therapy nor that reducing MAC is not a laudable goal. Rather, the critical question is, why should we embrace molecular biology techniques to achieve these ends? In general, the only reason to use any new therapy is because it is more effective, has fewer side effects, is easier to use, or is less expensive than traditional therapies. A close look at these issues suggests that “gene therapy” may not offer clinical anesthesia as much as it offers other medical disciplines.

Consider the issue of efficacy. As the authors’ reference list makes clear, several investigators have shown previously that blockade of NMDA receptors using receptor-specific antagonists reduces isoflurane MAC as much as do antisense oligonucleotides.\(^5\)\(^,\)\(^6\) Similarly, more than a decade ago, Drasner *et al.*\(^7\) showed that stimulation of spinal \(\mu\)-opioid receptors with intrathecal morphine reduces halothane MAC by more than 40% in humans. More recently, Hodgson *et al.*\(^7\) showed that epidural anesthesia reduces isoflurane MAC by approximately 50% in humans.\(^8\) Clearly, it is not necessary to administer antisense oligonucleotides to affect marked reductions in isoflurane MAC, but doing so could be justified if this approach conferred other important clinical advantages over currently available techniques. Because the study of Tao and Johns was not meant to be applied clinically, it did not include a group of animals treated with one of these “traditional” pharmacologic approaches to reduce isoflurane MAC. However, such control groups are essential in future studies hoping to

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**Accepted for publication February 28, 2001. The author is not supported by, not maintains any financial interest in, any commercial activity that may be associated with the topic of this article.**

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This Editorial View accompanies the following article: Tao Y-X, Johns RA: Effect of the deficiency of spinal PSD-95/SAP90 on the minimum alveolar anesthetic concentration of isoflurane in rats. Anesthesiology 2001; 94:1010–5. Interested readers should also see the article entitled “Gene Therapy for the Management of Pain, Part I: Methods and Strategies” by Wu *et al.*, also in this issue of Anesthesiology, pages 1119–32.
carve a clinical niche for genetic techniques so that we can rationally compare not only the relative efficacy of genetic and traditional pharmacotherapies, but also side effect profiles. Although Tao and Johns report no obvious side effects from knockdown of PSD-95/SAP 90 in their study, the testing methods were sensitive only to gross locomotor changes, and rats may be more tolerant to subtle, unpleasant sensorimotor changes than humans are.

Ease of use is another important factor that does not favor the clinical use of genetic therapies in anesthesia. Traditional receptor agonists and antagonists are effective immediately after administration, whereas antisense oligonucleotides require days of repeated administration (4 days in the study of Tao and Johns) to reduce protein number sufficiently to achieve the desired effect. In addition to a slow onset of action, antisense techniques also have a relatively slow offset that depends on both the rate at which the antisense oligonucleotide is eliminated and the basal turnover rate of the target protein. Although offset rate varies by protein, in some cases, it will be measured in days, not hours. This prolonged duration of action certainly will be of benefit in some settings but will be a liability in the patient who has intolerable side effects or who simply needs to recover sufficient function to be discharged from the hospital. In addition, antisense effects will not be amenable to antagonism in the same way we use drugs such as naloxone or flumazenil to competitively antagonize the effects of opioid and benzodiazepine receptor agonists.

These caveats are not to suggest that anesthesiology will not benefit from the expansion in pharmaceutical approaches to control gene expression. Nevertheless, the acute nature of most of our clinical practice will limit their applicability. However, as Tao and Johns suggest, subacute and chronic pain areas are in which techniques to control gene expression may bring important benefits to patients. We now appreciate that the central nervous system is “plastic” and that the intense afferent sensory barrage that hits the spinal cord during tissue injury (e.g., surgery or trauma) can cause persistent changes at the synaptic level that result in increased or persistent pain.10–11 Phenomena such as long-term potentiation, long-term depression, allodynia, and hyperalgesia all involve changes in gene expression that are potentially amenable to control by biopharmaceuticals that alter protein synthesis. One can easily envision a day when patients who come to the operating room for amputation will receive a cocktail that includes a local anesthetic for the procedure, an opioid for early postoperative pain relief, and antisense oligonucleotides to prevent the neuroplastic changes that cause phantom limb pain.

Today, it seems that gene therapy may be in our future, albeit in a very limited way. It likely will come slowly to our discipline because the economics of anesthetic drugs is such that drug companies will not be rushing to market with novel gene therapies for our use (the worldwide market value of all anesthetic drugs is less than the value of the US salsa market). To hasten the development of molecular biopharmaceuticals for our patients, it is essential that we clearly define those areas in which “gene therapy” confers a clear clinical advantage over traditional treatments. To this end, both clinical and basic science researchers need to include “traditional” pharmacologic control groups in their studies whenever possible, and anesthesiologists need to educate themselves about molecular biology so they can determine whether and when gene-directed pharmacology offers advantages over traditional pharmacology.

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References