

CORRESPONDENCE

Anesthesiology
79:631, 1993
© 1993 American Society of Anesthesiologists, Inc.
J. B. Lippincott Company, Philadelphia

The Importance of *In Vitro* Assay Temperature When Using Volatile Anesthetics

To the Editor:—The recent report by El-Maghrabi and Eckenhoff demonstrated that halothane and isoflurane disrupted [³H]dopamine transport into synaptosomes from rat brain.¹ The authors suggest that the clinical relevance of this observation is validated, at least in part, by the fact that the IC₅₀ of the inhibition by halothane was 0.7 mM at 22° C. Equilibration of 1% v/v halothane (1 MAC in rats)² with Tris buffer at 37° C results in an aqueous halothane concentration of 0.4 mM.³

We believe that the extrapolation of results obtained using volatile anesthetics at below physiologic temperatures must be qualified before any claim of clinical relevance can be maintained. Inhibition of amine transport by halothane at physiologic temperature would hold more credence with regard to clinical relevance than would similar inhibition at room temperature. That amine transport processes are temperature-dependent leads us to only speculate as to why the authors failed to measure anesthetic influences on dopamine transport at 37° C.

We maintain that this shortcoming fails to allow any valid extension of these results to the *in vivo* situation. In reporting the inhibition of [³H]5-hydroxytryptamine (5-HT) transport by halothane at 37° C, we noted a somewhat less potent effect than the present results, where the IC₅₀ value for halothane was approximately 1.0 mM.⁴ Moreover, contrary to what El-Maghrabi and Eckenhoff stated, we noted a competitive kinetic interaction between halothane and 5-HT transport, implying an action by the anesthetic at the 5-HT transport recognition site.

Anesthesiology
79:631-632, 1993
© 1993 American Society of Anesthesiologists, Inc.
J. B. Lippincott Company, Philadelphia

In Reply:—Martin and Merin raise at least two temperature-related issues, one being the influence of temperature on transport processes and the other being the relationship between temperature and volatile anesthetic concentration. There is no question that dopamine transport is temperature-dependent. This is the reason why the kinetic assays reported in our paper¹ were performed at 37° C; a fact clearly stated in the methods section. Only the inhibition experiments were performed at 22° C—to slow the initial rate of uptake and reduce the time-dependency of the assay. We have made the reasonable assumption that the IC₅₀ value is *temperature-independent*, as verified by our finding that V_{max} in the presence of anesthetics (at 37° C) was reduced by an amount predicted by the 22° C IC₅₀.¹

To examine the issue of temperature dependence of anesthetic concentrations, it is important to remember that anesthetic effects are ultimately related to the *molar concentration*, and not the gas

Dan C. Martin, M.D.
Associate Professor
Departments of Anesthesiology
and Pharmacology and Toxicology

Robert G. Merin, M.D.
Professor
Department of Anesthesiology

Medical College of Georgia
Augusta, Georgia 30912-2700

References

1. El-Maghrabi EA, Eckenhoff RG: Inhibition of dopamine transport in rat brain synaptosomes by volatile anesthetics. *ANESTHESIOLOGY* 78:750-756, 1993
2. Mazze RI, Rice SA, Baden JM: Halothane, isoflurane, and enflurane MAC in pregnant and nonpregnant female and male mice and rats. *ANESTHESIOLOGY* 62:339-341, 1985
3. Martin DC, Pruetz JK, Aronstam RS: Test-tube equilibration of volatile anaesthetic concentrations. *Br J Anaesth* 70:365-367, 1993
4. Martin DC, Adams RJ, Introna RPS: Halothane inhibits 5-hydroxytryptamine uptake by synaptosomes from rat brain. *Neuropharmacology* 29:9-16, 1990

(Accepted for publication June 22, 1993.)

concentration, despite the anesthesiologists' fixation on minimum alveolar concentration (really a compromise for measurement convenience and generally valid because of the relatively constant temperature of our patients). If the molar concentration is produced by equilibration with a gas phase, then temperature is important, because of the temperature-dependent nature of blood or buffer/gas partition coefficients. For example, 0.35 mM halothane in Kreb's buffer is produced by equilibration with about 1.0 vol% at 37° C or 0.5 vol% at 22° C. However, if the anesthetic is dissolved directly in a gas-tight system with no gas space (as we did), then the molar concentration is *temperature-independent*. Because most potency data for these agents are expressed in vol%, it is necessary for laboratory investigators to relate the (measured) molar concentration back to the clinically familiar gas concentration. In doing so, it is crucial that 37° C partition coefficients be used, regardless of the actual experiment's tempera-