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## From Bench to Bedside and Back Again: A Personal Journey with Dexmedetomidine

Mervyn Maze, M.B., Ch.B.\*

\*William K. Hamilton Distinguished Professor of Anesthesia, Department of Anesthesia and Perioperative Care, University of California, San Francisco, San Francisco, California

The effect of 4(5)-[1-(2,3-dimethylphenyl)ethyl]imidazole (dexmedetomidine), the  $\alpha_2$  adrenergic agonist, on anesthetic requirements was investigated in rats anesthetized with halothane. Halothane MAC was determined before and after either dexmedetomidine (d-enantiomer) or levomedetomidine (l-enantiomer) 10, 30, and 100  $\mu\text{g}/\text{kg}$  or vehicle ip. There was a dose-dependent increase in MAC with the d-, but not the l-, stereoisomer. At the highest dose of dexmedetomidine (100  $\mu\text{g}/\text{kg}$ ), halothane could be discontinued for up to 30 min with no response to tail clamping. To determine whether  $\alpha_2$  adrenoreceptors mediated this effect of dexmedetomidine on MAC, cohorts of rats were pretreated with idazoxan, 10 mg/kg ip, a highly selective  $\alpha_2$  antagonist. This completely prevented the reduction of MAC caused by dexmedetomidine. To determine whether the reduction of MAC caused by dexmedetomidine was mediated in part through either opiate or adenosine receptors, groups of rats were pretreated with either naltrexone, 5 mg/kg ip, an opiate antagonist, or 8-phenyltheophylline, 2.5 mg/kg ip, an  $A_1$  adenosine antagonist. These two pretreatments did not alter the reduction of MAC by dexmedetomidine. To determine whether postsynaptic mechanisms mediate the anesthetic effect of dexmedetomidine, rats were depleted of central catecholamine stores with either n-(2-chloroethyl)-n-ethyl-2-bromobenzylamine (DSP-4) or reserpine and alpha-methyl-para-tyrosine and MAC was determined before and after each dose of dexmedetomidine. While the catecholamine-depleted rats had a lower basal MAC than the vehicle controls, there was still a profound reduction in halothane MAC after administration of dexmedetomidine. The reduction of MAC by dexmedetomidine was blocked with idazoxan in the catecholamine-depleted rats. These data indicate that the reduction of MAC caused by dexmedetomidine is mediated through  $\alpha_2$  adrenoreceptors with no apparent involvement of either opiate or  $A_1$  adenosine receptors. Data from catecholamine-depleted rats suggest that the mediating mechanism must involve site(s) other than or in addition to the presynaptic  $\alpha_2$  adrenergic receptors on noradrenergic neurons. The authors conclude that central postsynaptic  $\alpha_2$  adrenergic receptors mediate a significant part of the reduction of anesthetic requirements caused by dexmedetomidine.

It is with equal measures of pride, humility, and trepidation that I agreed to revisit what is now referred to as a Classic Paper.<sup>1</sup> In 1985 I was seeking a way to distinguish my academic

Address correspondence to Dr. Maze: Department of Anesthesia and Perioperative Care, University of California, San Francisco, 1001 Potrero Avenue, Box 1363, San Francisco, CA 94143, Phone: 415-206-8906, mervyn.maze@ucsf.edu.

career for an upcoming date with the tenure process at Stanford University. I secured a sabbatical in the Department of Physiology and Pharmacology at the Karolinska Institutet (Stockholm, Sweden) in 1986 to learn the then-novel microdialysis technique for monitoring in vivo neurotransmission in discrete loci within the brain. Together with interventions that acutely changed noradrenergic neurotransmission, I would then be in a position to directly test the hypothesis that central noradrenergic neurotransmission regulated anesthetic depth. On my return from sabbatical while visiting a postoperative patient in one of the pre-fabricated satellite buildings at the pre-earthquake Palo Alto Veterans Administration Medical Center (PAVAMC), I had a chance encounter with a Stanford-trained psychiatrist, John Csernansky, M.D. (Chair, Department of Psychiatry and Behavioral Sciences, Northwestern University, Chicago, Illinois). John told me about a recent visitor from Turku, Finland, who was a research pharmacologist from Farnos Group Ltd., Risto Lammintausta, M.D., Ph.D., (currently CEO, Forendo Pharma, Turku, Finland). Dr. Lammintausta had synthesized medetomidine, a very potent alpha-2 adrenergic agonist that had become an attractive candidate with which to test the above-mentioned hypothesis, as we had just completed a series of experiments with another of that drug class, azepexole, demonstrating its impressive MAC-reducing properties.<sup>2</sup> I secured a sample of medetomidine (the racemic mixture of D and L stereoisomers) from Dr. Lammintausta, and started a series of experiments with Ross G. Vickery, Ph.D. (Department of Clinical Pharmacology and Experimental Medicine, Theravance, Inc., South San Francisco, California), then a newly minted B.S. graduate from Stanford, who went on to study post-receptor ion channel signaling in G protein-coupled receptors. We undertook a comparable preclinical study to the one with azepexole and found that the first medetomidine-exposed subject remained unarousable to painful stimuli even after the volatile anesthetic had been reduced to “0” for greater than 1 hour! Because animals that were entirely depleted of norepinephrine (i.e., zero noradrenergic neurotransmission) are not anesthetized,<sup>3</sup> there had to be another mechanism to explain the MAC-eliminating observation with medetomidine. To rule out an off-target effect, we administered a selective alpha-2 antagonist, yohimbine. In a Eureka moment, the previously unarousable dog immediately awoke, leaving a relieved Ross to cope with a now-frisky animal!

We reasoned that the anesthetic-inducing effect of medetomidine was an alpha-2 response but did not think that it was exclusively due to a presynaptic decrease in noradrenergic neurotransmission. At that juncture, Ira S. Segal, M.D. (Consultant Anesthesiologist, Southdale Anesthesiologists LLC, South Edina, Minnesota), then a recently trained anesthesiologist, approached me to study the mechanism of anesthetic action, and I told him about the recent observation. We decided to change the experimental species from dogs to rats because the slew of experiments needed to resolve the looming questions was going to bankrupt my laboratory unless we used less expensive reagents. Using what was considered state-of-the-art technology (that now seems quite primitive), we ruled out the pre-synaptic receptors that left open the possibility that medetomidine produced anesthesia through a direct action on postsynaptic receptors.<sup>1</sup> As Farnos had since resolved the racemic mixture into the L and D isomers of medetomidine, we were also able to identify that the action was stereospecific with only the D isomer exerting hypnotic-anesthetic action (**fig. 1**). Collectively, these observations formed the basis for a use patent of dexmedetomidine that

Mika Scheinin, M.D., Ph.D. (Professor, Department of Clinical Pharmacology, University of Turku, Finland) and I filed jointly (CA 1338556 C<sup>4</sup>); the patent was reassigned to Farnos for the princely sum of \$250,000 that Stanford was gracious enough to return to my laboratory.

With that largesse, we were able to pursue studies, including with Brian K. Kobilka, M.D. (Professor, Department of Molecular and Cellular Physiology, Stanford University, Stanford, California; 2012 Nobel Laureate in Chemistry) and Lee E. Limbird, Ph.D. (Professor of Biochemistry, Fisk University, Nashville, Tennessee; Editor, Goodman and Gilman's Manual of Pharmacology and Therapeutics), to define the site, structure and signal transduction mechanisms for dexmedetomidine's hypnotic-anesthetic action.<sup>5-9</sup> Armed with this knowledge, Brian Kobilka, Michael Levitt, Ph.D. (Professor of Structural Biology, Stanford University, Stanford, California; 2013 Nobel Laureate in Chemistry), and I briefly entertained the idea of a Stanford start-up company that would use structural biology and high-throughput screening to synthesize and screen the next generation of highly-selective alpha-2 adrenergic agonists; however, no venture capitalist wanted to risk their money on a trio of ne'er-do-wells!

We entered into a stage of clinical investigation in which we collaborated with the group at University of California, Los Angeles who had pursued the perioperative use of clonidine, another alpha-2 agonist;<sup>10</sup> our University of California, Los Angeles collaborators included the gifted pharmacologist, Byron Bloor, M.D., who was tragically killed in a boating accident soon after completing a seminal series of volunteer studies.<sup>11,12</sup> By then we were pursuing a route-to-market authorization that required key pharmacokinetic and pharmacodynamic studies, ably supervised by Steven Shafer, M.D. (Professor of Anesthesiology, Perioperative and Pain Medicine, Stanford University, Stanford, California), a PAVAMC collaborator.<sup>13,14</sup> Par for the course in that era of volunteer investigation, we recruited residents from our training program in whom we were unable to identify a dexmedetomidine electroencephalogram profile because it so closely resembled their baseline—a state of exhaustion from sleep deprivation! The similarity between dexmedetomidine sedation and natural sleep was subsequently established by two graduate students at Imperial College in London: Laura Nelson Carney, Ph.D. (currently Mentor, Center for Entrepreneurship, The Chinese University of Hong Kong, Shatin, Hong Kong), in rats,<sup>15</sup> and Robert Sanders, M.B.B.S., Ph.D. (currently Assistant Professor, Department of Anesthesiology, University of Wisconsin, Madison, Wisconsin), in humans.<sup>16</sup> One of the recruited volunteers had an 11.5-second period of sinus arrest with no cerebral blood flow, but was able to recall the frenetic conversation that I had with the research nurse about administering glycopyrrolate through the pulmonary artery catheter. Again, this vagomimetic feature would teach us plenty about dexmedetomidine (vide infra) and left some wondering whether one could complete anesthesia training at Stanford without cerebral blood flow; the volunteer did and is now an Associate Professor at a prestigious institution.

Finally, we were ready for a Phase 3 pivotal trial; however, there was no consensus regarding which of the pleiotropic properties of dexmedetomidine should be the basis for the clinical label. Enter Romeo Bachand, M.D., Ph.D. (Chief Scientific Officer, Kenna Technologies,

Inc., West Chester, Pennsylvania), then a consultant for Abbott Laboratories, who led ~1,000-patient trials within the space of 12 weeks that established the efficacy and safety of dexmedetomidine as a sedative for no more than 24 hours during mechanical ventilation in mostly cardiac surgical patients. While the Food and Drug Administration rapidly approved the New Drug Application for Precedex™, the European Medicine's Agency requested further comparative outcome studies with the other commonly used sedatives, propofol and midazolam, which resulted in a decade-long delay to market authorization of Dexdor (trade name for dexmedetomidine in Europe).

Since the introduction of dexmedetomidine into clinical practice in 1999, there have been more than 600 published clinical trials culminating with the recent demonstration of the efficacy of dexmedetomidine in agitated, delirious patients.<sup>17</sup> The interest in the use of dexmedetomidine for extremely ill patients in the intensive care unit (ICU) may have had its genesis from a series of studies arising from an extremely fruitful collaboration with the outstanding biophysicist, Nicholas Franks, Ph.D. (Professor of Biophysics and Anaesthetics, Imperial College, London, England), who has devoted his entire academic life to understanding the molecular foundation for anesthetic action. These and subsequent studies provide the scientific underpinnings for the similarity that had been noted earlier between natural sleep and dexmedetomidine-induced sedation;<sup>15,18</sup> with this foundation, clinical studies were launched to exploit the restorative properties of a pharmacoinduced natural sleep.

Pratik Pandharipande, M.D. (Professor of Anesthesiology and Surgery, Vanderbilt University, Nashville, Tennessee) and E. Wesley Ely, M.D. (Professor of Medicine, Vanderbilt University, Nashville, Tennessee) were seeking an intervention to decrease the delirium in ICU patients that resulted in substantial morbidity and mortality, as well as incremental costs associated with prolonged stays in the ICU. In the first of many such studies, they demonstrated an increase in coma- and delirium-free days with dexmedetomidine-based sedation when compared to lorazepam, which at that time was the most frequently used ICU sedative.<sup>19</sup> In an a priori-designed analysis, Pratik showed that all-cause mortality could be improved with dexmedetomidine in a septic subset of patients from the MENDS study;<sup>20</sup> this finding is now being investigated in the National Institutes of Health-supported MENDSII trial comparing sedation with dexmedetomidine to that provided by propofol in septic patients.<sup>21</sup> Recent trials continue to further explore how to harness dexmedetomidine's benefits for a wider range of patients in the critical care environment.<sup>17,22</sup>

The foundation for dexmedetomidine's effect on survival may have had its basis in the earlier observation of its vagomimetic properties, because perioperative vagal activation is a key homeostatic process to resolve inflammation;<sup>23</sup> this inflammation-resolving property is beneficial in preclinical models of brain<sup>24</sup> and kidney<sup>25</sup> injury. Dexmedetomidine's benefit in models of brain injury inspired Robert Sanders to explore, and subsequently demonstrate, its role in improving anesthetic-induced developmental neurotoxicity.<sup>26</sup> A basic science consortium under the auspices of SmartTots is now optimizing the utility of dexmedetomidine in preclinical models for subsequent clinical trials as an adjuvant to enhance the safety of pediatric anesthetic regimens.

My experience in investigating dexmedetomidine has enriched my academic career, from the many eminent collaborators with whom I now have enduring friendships, to the 74 publications and countless speaking opportunities that these collaborative studies engendered. Early on, however, it did not seem such a good idea! My manuscript productivity was thwarted by delays to file patents leaving Stanford to ask for evidence why I should become a tenured professor! Investigating dexmedetomidine was my first endeavor in drug discovery and development, and having been bitten by that alluring bug, it has proven not to be my last with current efforts to derive clinical benefit from xenon, as well as strategies to combat postoperative cognitive decline.<sup>27,28</sup>

Reduced to its foundations, our clinical specialty is applied pharmacology, and I await many more pharmacology-based discoveries from the realms of its practitioners.

## Biography

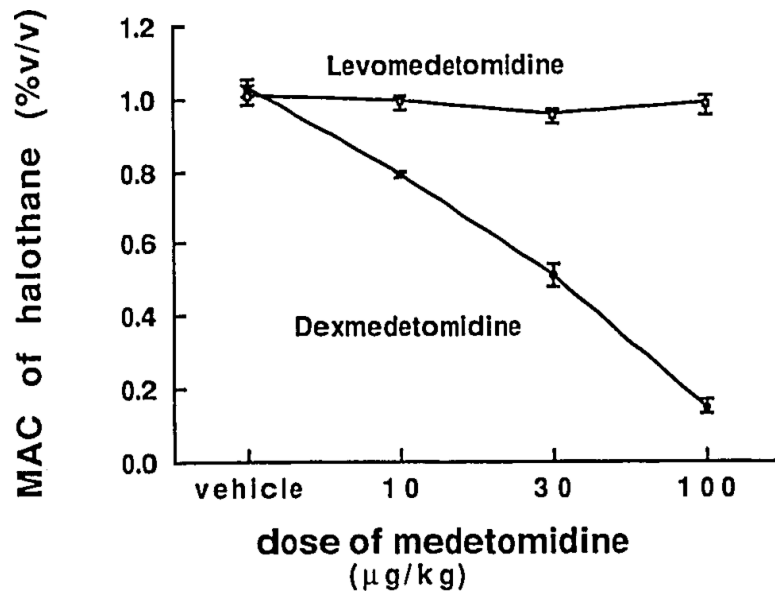


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**Fig. 1.** Effect of stereoisomers of the  $\alpha_2$  adrenergic agonist, medetomidine, on halothane MAC in rats. The MAC for halothane was determined in rats before and after either the d- (dexmedetomidine) (●) or the l- (levomedetomidine) (□) stereoisomer, 10, 30, and 100  $\mu\text{g/kg}$  ip. At each dose, ten rats were tested. Reprinted with permission from Segal IS, Vickery RG, Walton JK, Doze VA, Maze M: Dexmedetomidine diminishes halothane anesthetic requirements in rats through a postsynaptic  $\alpha_2$  adrenergic receptor. *Anesthesiology* 1988; 69:818-23