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Max Kelz, M.D., Ph.D., Recipient of the 2010 Presidential Scholar Award

Lee A. Fleisher, M.D.*

MAX Kelz, the 2010 recipient of the Presidential Scholar Award, is a wonderful testament to the ability of physician-scientists in anesthesiology to work on problems that affect questions of anesthesiology and general scientific interest. Max discovered his passion for scientific research early on. Under the tutelage of Mephi Ngoi, Ph.D. (Evanston Township High School, Evanston, Illinois), as a junior at Evanston Township High School, Max won early recognition for an organic chemistry project in the Westinghouse Science Talent search. He spent his summers at Northwestern University working in astrophysics as a member of Dr. Melville Ulmer's (Melville Ulmer, Ph.D., Professor, Dearborn Observatory, Department of Physics and Astronomy, Northwestern University, Evanston, IL) team that developed software tools for NASA's Compton γ-Ray Observatory, the second of NASA's great observatories. Max enrolled in college at Yale University and majored in molecular biophysics and biochemistry. As an undergraduate at Yale, he joined the laboratory of Eric Nestler, M.D., Ph.D. (Chair of Neuroscience, Mount Sinai Medical Center, New York, New York). Max became interested in the molecular mechanisms through which changes in gene expression alter complex traits such as behavior. In Dr. Nestler's laboratory, Max helped to discover that repeated exposure to cocaine and, subsequently, to all other known drugs of abuse, causes the induction and accumulation of a novel transcription factor, ΔFosB, in neuronal pathways that motivate endogenous rewards.[1–5] As a transcription factor with the potential to orchestrate changes in a host of downstream genes, ΔFosB proved to be an exciting target.[6] Max graduated from Yale with his bachelor's and master's degrees and was awarded a Richter Fellowship as well as the B. Edward Bensigner III Prize for his research. Upon graduation, Max elected to remain in New Haven for a combined M.D./Ph.D. program. He continued in Dr. Nestler's laboratory probing deeper into the functional significance of the molecular adaptations that accompany the drug addict state. His Ph.D. thesis in neuroscience was one of the early applications of tissue-specific inducible gene expression in the mouse central nervous system. Max demonstrated that direct accumulation of ΔFosB in reward pathways, including the nucleus accumbens, caused a predilection to cocaine addiction.[7] Subsequent studies also confirmed that accumulation of ΔFosB in these reward circuits predisposed to opiate and nicotine addiction as well.[8] Max's Ph.D. work won the prize for "Best Thesis" in his graduating class at Yale.

Max Kelz, M.D., Ph.D., recipient of the American Society of Anesthesiologists 2010 Presidential Scholar Award.

Max initially anticipated a clinician scientist's career in psychiatry or neurology. However, the exposure to the field of anesthesiology as a medical student at Yale highlighted by the exquisite teaching of Keith Ruskin, M.D. (Assistant Professor of Anesthesiology, Yale University School of Medicine, New Haven, Connecticut), and Will Rosenblatt, M.D. (Professor of Anesthesiology and of Surgery [Otolaryngology], Yale University School of Medicine, New Haven, Con-

* Robert D. Dripps Professor of Anesthesiology and Critical Care, Department of Anesthesiology and Critical Care, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania.

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necticut), helped convince Max that anesthesiology was a perfect field. Clinically, Max was twice recognized as a Farr Scholar. He joined his medical school classmate and wife, Rachel Rapaport Kelz, at the University of Pennsylvania, where he began residency training. Ongoing exposure to outstanding clinicians and scientists at Penn and lively discussions with his role models, David Eckmann, Ph.D., M.D. (Horatio C. Wood Professor of Anesthesiology and Critical Care, Penn Medicine, Philadelphia, Pennsylvania), and Roderic Eckenhoff, M.D. (Austin Lamont Professor of Anesthesiology and Critical Care, Penn Medicine, Philadelphia, Pennsylvania), inside and outside of the operating rooms, continued to fuel Max's scientific drive. Max worked in the laboratory of Jim Eberwine, Ph.D. (Professor, Department of Pharmacology, Mahoney Institute of Neurologic Sciences at the University of Pennsylvania, Philadelphia, Pennsylvania), in the Department of Pharmacology at Penn as a postdoctoral fellow during his internship and residency where he studied single-cell genomics.[9]

As a resident at Penn, Max encountered an otherwise healthy patient with narcolepsy and cataplexy who took more than 7 h to emerge from a standard inhaled general anesthetic. This case sparked Max's interest in the regulation of arousal state control and the actions of anesthetic drugs on endogenous neuronal circuits. Because the underlying genetic basis of narcolepsy with cataplexy had just been discovered to be impaired signaling in the wake promoting and sustaining hypocretin/orexin system,[10–12] and because there are only a few thousand hypocretin/orexin neurons all confined to the hypothalamus, Max pursued the hypothesis that inhaled anesthetics should inhibit the activity of hypocretin/orexin neurons, their excitatory afferents, or their efferents, leading to delayed anesthetic emergence. With the generous support of the Foundation for Anesthesia Education and Research and the Department of Anesthesiology and Critical Care at Penn, Max joined the faculty as an assistant professor in 2004 in the tenure track. Under the guidance of his comentors, Rod Eckenhoff in anesthesiology and Sigrid Veasey, M.D., D.A.B.S.M. (Associate Professor of Medicine, Penn Medicine, Philadelphia, Pennsylvania), in the Department of Medicine and the Center for Sleep and Respiratory Neurobiology, Max was awarded a National Institutes of Health K08 grant from the National Institute of General Medical Sciences to pursue the interactions of anesthetics with the hypocretin/orexin system. He built custom high-throughput models to accelerate anesthetic phenotyping of genetically engineered mice behaviorally[13,14] and electroencephalographically.[15]

Using a mouse model system of narcolepsy and cataplexy in collaboration with the Yanagisawa laboratory, Max demonstrated that isoflurane and sevoflurane do indeed inhibit hypocretin/orexin neurons but do not affect activity in neighboring neurons. Moreover, this work demonstrated that narcoleptic mice also exhibited delayed emergence from the halogenated ether anesthetics.[16] These findings encouraged Max to follow the overreaching hypothesis that the hypnotic component of general anesthesia arises when anesthetic drugs hijack endogenous sleep-wake circuits.[17,18] However, just as decades of research have highlighted the stunning complexity in potential molecular targets of anesthetic action, studies by Max and others are beginning to highlight the diversity of distinct anesthetic agents upon specific neuronal targets, including the hypocretin/orexin system.[19,20]

Building upon the orexin/hypocretin work, Max has hypothesized that the forward and reverse processes through which the state of anesthesia arises and dissipates need not be identical. He has convincingly shown that hysteresis for anesthesia induction and emergence exists in multiple species and cannot be explained purely by pharmacokinetics. He has termed this barrier to arousal-state change as "neural inertia," and it has many implications to clinical practice as well as to the fundamental neurobiology of consciousness. His questions have taken him from the hyperbaric chamber to *Drosophila*, bringing new collaborations back to anesthesiology and reinvigorating the intellectual curiosity and the scientific credibility of our discipline. Max was recently awarded a National Institute of General Medical Sciences R01, which continues to focus upon the interface between natural sleep and anesthesia. This grant will use electrophysiology in combination with classic and novel techniques to identify critical neuroanatomic substrates underlying volatile anesthetic hypnosis. Sheryl Beck, Ph.D. (Department of Anesthesiology and Critical Care, Penn Medicine, Philadelphia, Pennsylvania), has become an indispensable collaborator on these studies.

Max is also a great mentor, as evidenced by the numerous medical students and residents who have chosen to work with him. A Penn fourth-year medical student won "Best Thesis" Prize for his work on dexmedetomidine in Max's laboratory in 2007–2008. Several residents have gone on to win awards at the Pennsylvania Anesthesia Resident Conference. He also has the unique distinction of being the advisor for a neuroscience M.D./Ph.D. student who won the top research cash prize at the Sleep Retreat this year for his work. For someone at this stage of Max's career, this was a unique honor, and this student will hopefully be a future anesthesiologist/scientist based upon his interactions with Max.

In addition to his clinical acumen and his fundamental research, Max also excels at teaching. He is a sought-after lecturer in the University at large, in addition to his bedside teaching of the residents.

Max Kelz is a great example of a young physician-scientist/anesthesiologist and is a true triple threat. On top of that, he is one of the most collegial and friendly individuals and is always there to help a colleague, whether it be clinical, academic, or personal issues.

References

1. Chen J, Kelz MB, Hope BT, Nakabeppu Y, Nestler EJ: Chronic Fos-related antigens: Stable variants of deltaFosB induced in brain by chronic treatments. J Neurosci 1997; 17:4933–41

2. Nye HE, Hope BT, Kelz MB, Iadarola M, Nestler EJ: Pharmacological studies of the regulation of chronic FOS-related antigen induction by cocaine in the striatum and nucleus accumbens. J Pharmacol Exp Ther 1995; 275: 1671–80
3. Chen J, Nye HE, Kelz MB, Hiroi N, Nakabeppu Y, Hope BT, Nestler EJ: Regulation of delta FosB and FosB-like proteins by electroconvulsive seizure and cocaine treatments. Mol Pharmacol 1995; 48:880–9
4. Hope BT, Nye HE, Kelz MB, Self DW, Iadarola MJ, Nakabeppu Y, Duman RS, Nestler EJ: Induction of a long-lasting AP-1 complex composed of altered Fos-like proteins in brain by chronic cocaine and other chronic treatments. Neuron 1994; 13:1235–44
5. Hope BT, Kelz MB, Duman RS, Nestler EJ: Chronic electroconvulsive seizure (ECS) treatment results in expression of a long-lasting AP-1 complex in brain with altered composition and characteristics. J Neurosci 1994; 14:4318–28
6. Kelz MB, Nestler EJ: DeltaFosB: A molecular switch underlying long-term neural plasticity. Curr Opin Neurol 2000; 13:715–20
7. Kelz MB, Chen J, Carlezon WA Jr, Whisler K, Gilden L, Beckmann AM, Steffen C, Zhang YJ, Marotti L, Self DW, Tkatch T, Baranauskas G, Surmeier DJ, Neve RL, Duman RS, Picciotto MR, Nestler EJ: Expression of the transcription factor deltaFosB in the brain controls sensitivity to cocaine. Nature 1999; 401:272–6
8. Zachariou V, Bolanos CA, Selley DE, Theobald D, Cassidy MP, Kelz MB, Shaw-Lutchman T, Berton O, Sim-Selley LJ, Dileone RJ, Kumar A, Nestler EJ: An essential role for DeltaFosB in the nucleus accumbens in morphine action. Nat Neurosci 2006; 9:205–11
9. Kelz MB, Dent GW, Therianos S, Marciano PG, McIntosh TK, Coleman PD, Eberwine JH: Single-cell antisense RNA amplification and microarray analysis as a tool for studying neurological degeneration and restoration. Sci Aging Knowledge Environ 2002; 2002: re1
10. de Lecea L, Kilduff TS, Peyron C, Gao X, Foye PE, Danielson PE, Fukuhara C, Battenberg EL, Gautvik VT, Bartlett FS, 2nd, Frankel WN, van den Pol AN, Bloom FE, Gautvik KM, Sutcliffe JG: The hypocretins: Hypothalamus-specific peptides with neuroexcitatory activity. Proc Natl Acad Sci USA 1998; 95:322–7
11. Chemelli RM, Willie JT, Sinton CM, Elmquist JK, Scammell T, Lee C, Richardson JA, Williams SC, Xiong Y, Kisanuki Y, Fitch TE, Nakazato M, Hammer RE, Saper CB, Yanagisawa M: Narcolepsy in orexin knockout mice: Molecular genetics of sleep regulation. Cell 1999; 98:437–51
12. Lin L, Faraco J, Li R, Kadotani H, Rogers W, Lin X, Qiu X, de Jong PJ, Nishino S, Mignot E: The sleep disorder canine narcolepsy is caused by a mutation in the hypocretin (orexin) receptor 2 gene. Cell 1999; 98:365–76
13. Sun Y, Chen J, Pruckmayr G, Baumgardner JE, Eckmann DM, Eckenhoff RG, Kelz MB: High throughput modular chambers for rapid evaluation of anesthetic sensitivity. BMC Anesthesiol 2006; 6:13
14. Bianchi SL, Caltagarone BM, Oddo S, Laferla FM, Eckenhoff RG, Kelz MB: Inhaled anesthetic potency in aged Alzheimer mice. Anesth Analg 2010; 110:427–30
15. Leach NT, Sun Y, Michaud S, Zheng Y, Ligon KL, Ligon AH, Sander T, Korf BR, Lu W, Harris DJ, Gusella JF, Maas RL, Quade BJ, Cole AJ, Kelz MB, Morton CC: Disruption of diacylglycerol kinase delta (DGKD) associated with seizures in humans and mice. Am J Hum Genet 2007; 80: 792–9
16. Kelz MB, Sun Y, Chen J, Cheng Meng Q, Moore JT, Veasey SC, Dixon S, Thornton M, Funato H, Yanagisawa M: An essential role for orexins in emergence from general anesthesia. Proc Natl Acad Sci USA 2008; 105:1309–14
17. Lydic R, Biebuyck JF: Sleep neurobiology: Relevance for mechanistic studies of anaesthesia. Br J Anaesth 1994; 72:506–8
18. Nelson LE, Guo TZ, Lu J, Saper CB, Franks NP, Maze M: The sedative component of anesthesia is mediated by GABA(A) receptors in an endogenous sleep pathway. Nat Neurosci 2002; 5:979–84
19. Gompf H, Chen J, Sun Y, Yanagisawa M, Aston-Jones G, Kelz MB: Halothane-induced hypnosis is not accompanied by inactivation of orexinergic output in rodents. ANESTHESIOLOGY 2009; 111:1001–9
20. Zecharia AY, Nelson LE, Gent TC, Schumacher M, Jurd R, Rudolph U, Brickley SG, Maze M, Franks NP: The involvement of hypothalamic sleep pathways in general anesthesia: Testing the hypothesis using the GABAA receptor beta3N265M knock-in mouse. J Neurosci 2009; 29: 2177–87