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Neurochemical effects of anesthetic agents: implications for toxicity, addiction and cognitive dysfunction

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A recent Op Ed in the New York Times (February 23, 2013, David Engleman) aptly summarized the complexity of the human brain. «The Brain is composed of ~86 billion electrically active neurons, each connected to many thousands of neighbors. Each neuron relays information in the form of miniature voltage spikes, which are then converted into chemical signals that bridge the gap to other neurons. Most neurons send these signals many times per second. The complexity of such a system bankrupts our language; with our current technologies, we mostly detect an enigmatic uproar.»

«A new kind of science is required, one that can track and analyze the activity of billions of neurons simultaneously.» Thus, the Obama administration's support for study of functional connectivity in the human brain. This represents the new paradigm for brain function in our century.

The paradigm shift responsible for the current broadening of interest for Anesthesiologists in the many neurological consequences of all of the cellular and subcellular effects of anesthetic agents is well discussed by Perouansky and by Ginosar and Binshtok in editorial comments on this article. (Perouansky M. «The Quest for a Unified Model of Anesthetic Action: A Century in Claude Bernard's Shadow.» Anesthesiology 2012;117:465-74) Perouansky suggests that we have been in thrall to Claude Bernard for the last century, trapped in a paradigm demanding a single mode of action to anesthetic agents, ignoring their protean effects on many aspects of cellular and enzymatic function. Franks and Lieb's[1] seminal observations of volatile anesthetic effects on protein, at hydrophobic - lipophilic and other molecular binding sites, has allowed us to move from the prior focus on lipid membrane effects of these agents, opening our minds to the multitude of actions of these agents on enzymes, on cellular function and on neurochemistry.

It is the intention in this lecture to outline aspects of recent work in neurochemistry and anesthesia, the implications for neurotoxicity, the involvement in addiction mechanisms, and in genesis of delirium and cognitive dysfunction.

NEUROCHEMISTRY AND ANESTHESIA

Recent evidence suggests that inhaled anesthetics exert specific actions on a number of critical molecular targets to create their clinical and behavioral effects[2], exerting different effects on different neural regions within the central nervous system. Evidence that inhaled anesthetics create immobilization, ablating movement in response to noxious stimuli, by depressing spinal cord functions, whereas they create amnesia and hypnosis by actions within the brain itself have been provided by several ingenious experiments utilizing separate delivery of agents either to the brain or to the spinal cord.[3] Specific proteomic targets for anesthetic action have been sought and a wide variety of protein interactions with volatile anesthetics explored since the seminal work of Franks and Lieb.[1] These targets include ion channels, cytoplasmic signaling proteins including protein kinase C and heme-binding sites, such as those on cytochrome P450 series enzymes and on guanylate cyclase. Linking the effects of anesthetics on these specific molecular targets to the behavioral effects of the anesthetics is a significant challenge. Data relating to regional neurochemical effects of anesthetics within the central nervous system will be essential.

Our goal is to develop a method for noninvasive, *in vivo* examination of regional neuromodulator and neurotransmitter storage, distribution, production and flux throughout the central nervous system, that may allow us to better understand the regional effects of anesthetic agents within the brain. The

tools currently available for this task include microdialysis and HPLC analyses of extracellular chemicals, and PET with Magnetic Resonance Spectroscopy and functional MRI.[4,5,6] We have used MRS methods. The radio frequency (rf) signals emitted from a region of interest when paramagnetic nuclei (^{31}phosphorus, ^{1}Hydrogen, ^{19}Fluorine and ^{13}carbon) are placed in a strong, uniform magnetic field and stimulated at their resonant frequencies allow derivation of specific magnetic resonance spectra. The signal obtained has a specific rf spectrum (frequency and amplitude) dependent on the chemical environment of the paramagnetic nucleus under study. Fourier transformation of the rf spectra allows picogram per milliliter estimation of certain chemical species within the region of interest. The technique is non-invasive and causes no tissue damage when performed *in vivo*, and can be used repetitively over time.

Functional Magnetic Resonance Imaging, which measures neuronal activity indirectly, through use of the blood-oxygen-level-dependent (BOLD) signal, is an additional tool. The BOLD signal's interpretation depends however on neurovascular coupling, which might be altered in normal ageing and by disease[(6)], and is certainly disrupted by exhibition of volatile anesthetic agents. We are currently pursuing studies *in vivo* using this technique (fMRI) to assess pathways involved in drug-seeking and drug dependent behavior in narcotic dependent man in collaboration with Dr. Mark Greenwald[(7)].

In pursuit of our primary goal, we have embarked on a series of preliminary experiments in rats to measure the effects of anesthesia on those neuro-chemicals which can be assessed using the proton spectrum. This is in collaboration with Drs. Galloway and Moore[(8)].

The proton spectrum permits measurement of a range of chemicals including lactate, glutamine, glutamate, N-acetyl-aspartate, GABA and glycine, plus creatine. 13 carbon labeled glucose turnover to glutamate and glutamine has been used to estimate *in vivo* the stoichiometric relationships between the glutamate-glutamine cycle (Vcyc) and glucose oxidation (CMR glc(ox))[(9)]. In addition neuroenergetics can be related to neuronal spiking frequency in cortical regional neurons and thus the relation:

$$\Delta \text{CMRO}_2\ \% \approx \Delta \text{CMR glc}\ \% \approx \Delta \text{Vcyc}\ \% \approx \Delta \nu\ \%$$

(CMR = cerebral metabolic rate, oxygen, O_2 or glucose, glc; Δ Vcyc = turnover rate of glutamatic acid and glutamine; and $\Delta \nu$ = neuronal spiking frequency)

has been inferred[(9)]. Our preliminary results from studies of halothane and isoflurane in rats will be presented[(10)] with these correlations in mind.

Previous work on the effects of anesthetics on uptake, synthesis and release of neurotransmitters has been reviewed[(11)]. Limited data has been obtained *in vivo* from humans. More recently, Wu and others[12] have shown in the calyx of Held, that isoflurane depresses presynaptic release of glutamate at an excitatory synapse. The authors[(12)] further explored the underlying mechanism finding that isoflurane depressed the action potential invading the presynaptic terminal, and have shown that this 5% decrease in action potential accounts for at least 70% of the decrease in glutamate release. The effects of this decrease in release on neuronal stores of glutamate or on the glutamate/glutamine cycle and glucose utilization have not yet been examined.

Furthermore, such data needs to be extended to other brain regions and to other neuromodulator and neurotransmitter receptor sets if we are to fully explore anesthetic mechanisms.

In order to understand the actions of anesthetics one must look at regional central nervous system functional anatomy and correlate the anesthetic perturbation of function with the chemical mechanisms[(13)]. Although general anesthesia and naturally occurring sleep both depress consciousness, it has been held that the two states differ. However, localization of brain nuclei involved in sleep have suggested that such nuclei may be important in anesthetic action.[14] Furthermore, interactions between sleep deprivation and anesthesia and the effects of anesthetic agents directly introduced into these nuclei appear to confirm these links[(14)]. Brain imaging evidence for a thalamocortical switch as a neurophysiologic basis for anesthetic-induced unconsciousness has also been proposed[(15)]. Positron Emission tomography and statistical parametric mapping techniques were used to measure regional cerebral glucose metabolism with 18 fluorodeoxyglucose in 11 young healthy right-handed male volunteers at baseline and then during anesthesia with halothane (N = 5) or isoflurane (N = 6). General anesthesia induced both global and specific regional reductions in brain glucose metabolism from baseline. These authors showed a significant conjoint effect between the two anesthetic agents such that both agents caused specific relative reductions of regional CMRglc in the thalamus, but also in the midbrain reticular formation, basal forebrain, cerebellum and occipital cortex. They then postulated a switch mechanism for the thalamus within thalamo-cortical, cortico-thalamic and reticulo-thalamic circuits, which might determine a change from consciousness to sleep or hypnosis from exposure to anesthetic agents[(15)]. An accompanying editorial[(16)] clearly explains the difficulties with this postulate as a unified theory for conscious awareness and argues for the provision of more empirical evidence to allow development of a wider range of theories and a clearer understanding of the neural substrate during anesthesia and sleep.

Microdialysis and extracellular fluid analyses[(17)] provide only partial data for some chemicals and are subject to significant potential for tissue damage and thus misinterpretation. Tools are soon at hand for the provision of further evidence of the effects of anesthesia on regional neurochemistry, which,

we believe, is a vital element in unraveling these intriguing questions in relation both to sleep and anesthesia[18,19], but also to neurotoxicity of the agents and their relationship to addiction, delirium and cognitive dysfunction[20].

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RECOMMENDED READING

1. Nature Collection - Chronic Pain. Eds Heather Wood and Darren Yates: The NIH Pain Consortium April 2013. Particularly S18 - "Can Neuroimaging Identify Pain Endophenotypes in Humans?" Originally published Nat Rev Neurol. 2011;7:173-81.