Probing for Functional Sites of Consciousness with Anesthetics: The Role of the Cytoskeleton

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Introduction
Microtubules, tubulin protein structures that are part of the neuron cytoskeleton, bind several volatile anesthetic agents. Dysfunction of microtubules has been shown to be involved in cognitive disorders such as Alzheimer’s disease and dementia as well as in schizophrenia and bipolar disorder. Recent evidence suggests a role for the cytoskeleton, including microtubules, as a guide for intracellular ion signaling between ionotropic receptors and the cell body [1]. We investigate the location of anesthetic binding to tubulin and the effect on microtubule function.

Methods
A model tubulin dimer, was used to create a two dimer system arranged in microtubule geometry. The two dimer system with added ions was solvated, minimized, equilibrated to 300 K, and run through a 5 ns molecular dynamics simulation in GROMACS using periodic boundaries mimicking microtubule protofilament geometry. Trajectories were clustered via RMSD and run through the surface geometry program PASS modified according to [2], which determines putative binding pockets by gauging pocket depth and surrounding methyl groups with probe spheres. Pockets shared among clusters were taken as preferred binding sites.

Results and Conclusions
Multiple binding sites were found over the tubulin dimer. The colchicine and GTP binding regions showed potential binding sites that were persistent over the entire simulation, while the GDP binding region showed a potential binding site persistent over 65% of the simulation. A potential binding site persistent over the entire simulation was also found on the tubulin surface near a region of positive residues known to affect C-terminal tail dynamics. C-terminal tails have been shown to be crucial to microtubule dynamics including polymerization and signaling [3]. This suggests that the effects of volatile anesthetics on microtubule dynamics may disrupt normal intracellular communication in neurons.

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