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Single Molecule Analysis of Serotonin Transporter Regulation Using Quantum Dots JERRY CHANG, Vanderbilt University, IAN TOMLINSON, MICHAEL WARNEMENT, ALESSANDRO USTIONE, ANA CARNEIRO, DAVID PISTON, RANDY BLAKELY, SANDRA ROSENTHAL — For the first time, we implement a novel, single molecule approach to define the localization and mobility of the brain's major target of widely prescribed antidepressant medications, the serotonin transporter (SERT). SERT labeled with single quantum dot (Qdot) revealed unsuspected features of transporter mobility with cholesterol-enriched membrane microdomains (often referred to as "lipid rafts") and cytoskeleton network linked to transporter activation. We document two pools of surface SERT proteins defined by their lateral mobility, one that exhibits relatively free diffusion in the plasma membrane and a second that displays significantly restricted mobility and localizes to cholesterol-enriched microdomains. Diffusion model prediction and instantaneous velocity analysis indicated that stimuli that act through p38 MAPK-dependent signaling pathways to activate SERT trigger rapid SERT movements within membrane microdomains. Cytoskeleton disruption showed that SERT lateral mobility behaves a membrane raft-constrained, cytoskeleton-associated manner. Our results identify an unsuspected aspect of neurotransmitter transporter regulation that we propose reflects the dissociation of inhibitory, SERT-associated cytoskeletal anchors.

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