

P014 Partitioning of the serotonin transporter into cholesterol-enriched lipid microdomains modulates transport of serotonin
Francesca Magnani, Clive Williams, and Jana Haase
Department of Biochemistry, Trinity College, Dublin 2, Ireland
Department of Biochemistry, Conway Institute, University College, Dublin 4, Ireland

The serotonin transporter (SERT) is an integral membrane protein responsible for the clearance of serotonin from the synaptic cleft following the release of the neurotransmitter. SERT plays a prominent role in the regulation of serotonergic neurotransmission and is a molecular target for multiple antidepressants as well as substances of abuse. Recently, the serotonergic system has been associated with neuropsychiatric symptoms in patients with Alzheimer's and Parkinson's disease. Here we show that SERT associates with cholesterol-enriched lipid rafts in both a heterologous expression system and rat brain, and that the inclusion of the transporter into lipid microdomains is critical for serotonin uptake activity. SERT is present in a subpopulation of lipid rafts, which is soluble in Triton X-100, but insoluble in other non-ionic detergents such as Brij 58. Desegregation of lipid rafts upon depletion of cellular cholesterol results in a decrease of serotonin transport capacity (V_{max}), due to the reduction of turnover number of serotonin transport. Our data suggest that the association of SERT with lipid rafts may represent a mechanism for regulating the transporter activity, and consequently serotonergic signalling in the central nervous system, through the modulation of the cholesterol content in the cell membrane. Furthermore, SERT-containing rafts are detected in both intracellular and cell surface fractions, suggesting that raft association may be important for trafficking and targeting of SERT.