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Precise measurements of cholesterol transport rates give new hope for Alzheimer's treatment

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Neutrons have shown the movement of cholesterol between and within cells takes far longer than previously thought. Findings could impact the treatment of a range of diseases linked to abnormal rates of cholesterol transfer.

Scientists using neutron scattering at the Institut Laue-Langevin (ILL) and at the NIST Center for Neutron Research have discovered that cholesterol moves far slower within and between cells than previously thought. Their findings reveal how different concentrations of cholesterol within cells are maintained and shed light on severe disorders linked to cholesterol transport abnormalities, including Alzheimer's, which may help in their treatment.

Cholesterol forms part of the outer membrane that surrounds every cell. It plays a vital role, carrying chemical and nerve signals around the body by insulating nerve fibres, and aids the production of important hormones. Maintaining the correct levels of cholesterol through redistribution between and within the cells is therefore vitally important. As well as Alzheimer's, abnormalities in cholesterol transport can lead to several other fatal diseases, such as atherosclerosis and various cardiovascular disorders.

The precise rate of cholesterol transport, measured by the time it takes for cholesterol to evenly distribute in a system, could be used for

developing new, improved treatments for these disorders. However, progress in this area had until now been hampered by the wide variation in the values obtained from previous studies, which cover five to six orders of magnitude and range from several hours to a few milliseconds.

However, using neutrons scattering, scientists from ILL, NIST, Argonne National Laboratory and the University of Illinois at Chicago have shown that these values are in the order of several hours, far slower than generally thought. In their experiments, the team added cholesterol-enriched donor vesicles to cholesterol-free acceptor vesicles and tracked the cholesterol as it redistributed between them using neutrons, which, like x-rays, can probe systems at the molecular scale.

The team was even able to account for the errors in previous results. For example, they showed that cyclodextrin, a ring-shaped glucose molecule used in many earlier experiments and thought not to interfere in the intra-membrane transport process, actually speeds up this rate by an order of magnitude.

Dr Lionel Porcar, scientist at ILL explains: “Inaccurate cholesterol transport rates from previous studies have hampered our understanding of how healthy concentrations of cholesterol within cells are maintained. However, with the non-invasive, in situ techniques offered by neutrons, we can remove the need for tagging substances, and are able to reveal the true rate of transport. This can shed critical light on intracellular transport disorders.”

One such disorder is Alzheimer’s, where problems in cholesterol production and transport in the brain can lead to build-ups of the peptide amyloid b (Ab), which causes Alzheimer’s disease. In addition, irregular cholesterol transport changes the neurochemistry of tau proteins found in neurons and throughout the central nervous system, a hallmark of Alzheimer’s.

Statin drugs used to lower cholesterol levels have been shown to protect against Alzheimer's. With more accurate figures for how cholesterol moves at the cellular level, Dr Porcar and his colleagues believe their findings will help improve the effectiveness of current treatments and open up avenues to creating new ones.

More information: Garg et al., Noninvasive Neutron Scattering Measurements Reveal Slower Cholesterol Transport in Model Lipid Membranes,
Biophysical Journal (2011), doi:10.1016/j.bpj.2011.06.014

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