Chemical 'supercharger' solves molecular membrane mystery

May 17 2023, by Jon Atherton

a

Golgi-like lipid membrane

b

ER-like lipid membrane

c

PM-like lipid membrane

d

Mitochondria-like lipid membrane

e

Synaptic vesicle-like lipid membrane- VAMP2

100 nm

f

Synaptic vesicle-like lipid membrane
50nm extrusion

g

Synaptic vesicle-like lipid membrane
100nm extrusion

h

Synaptic vesicle-like lipid membrane
200nm extrusion

50 nm

50 nm

50 nm
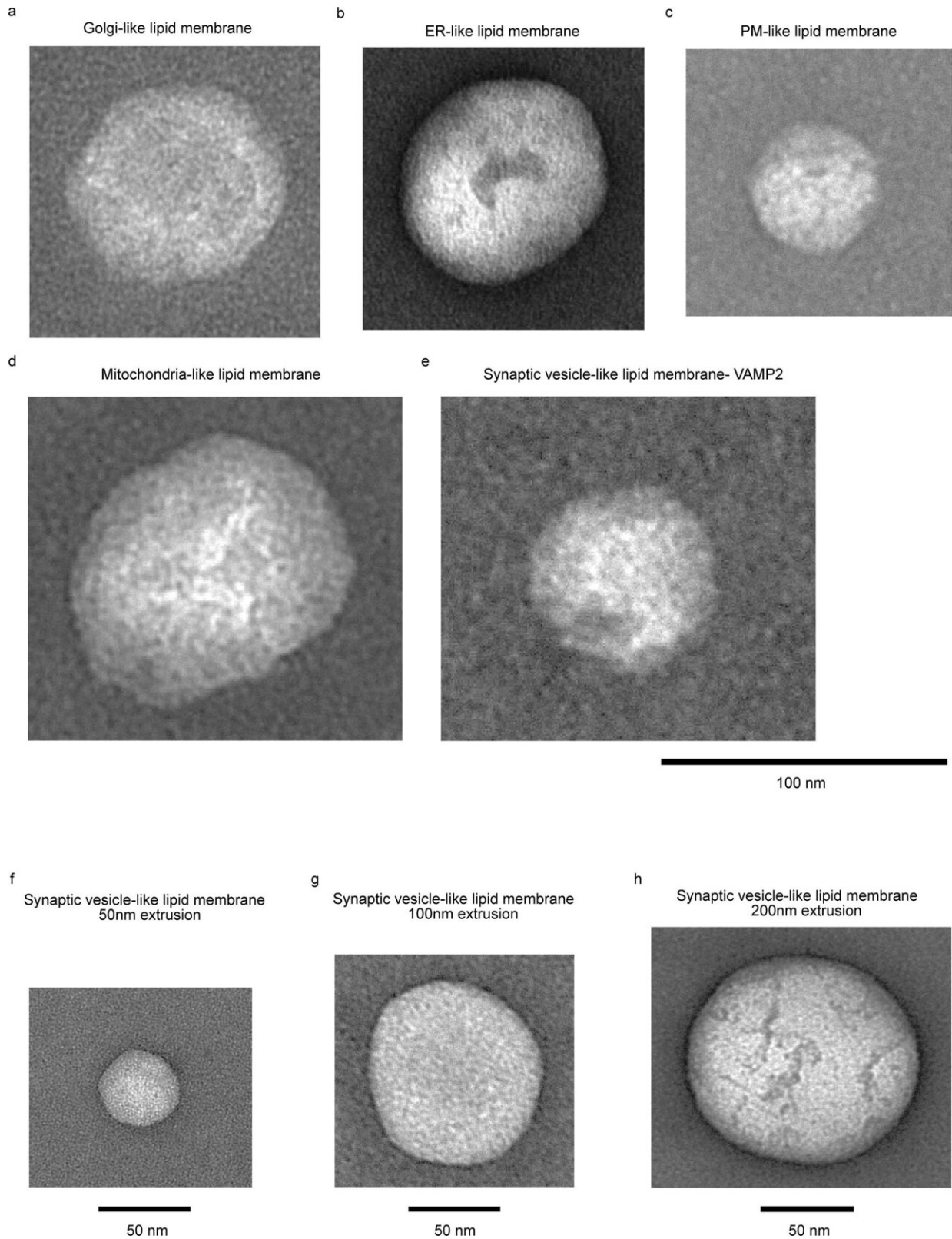
Negative stain TEM images of different lipid vesicles. a–e: Negative stain TEM

images of different lipid vesicles which mimics of different eukaryotic organellar membranes. f–h: Negative stain TEM images of different curvature synaptic vesicles. The desired curvature was achieved by passing the synaptic vesicles like lipid vesicles through different pore size membrane. All the sample was taken from a pool of vesicles that were subjected to nativeMS, confirming the vesicles in the samples. All measurements were replicated over three independent measurements. Credit: *Nature Methods* (2023). DOI: 10.1038/s41592-023-01864-5

Assemblies of tiny molecular proteins span the membranes that encapsulate our cells, directing cellular activities and regulating the transport of materials and information in and out.

In the fight against human disease, including various cancers and neurocognitive disorders, more than 60% of market drugs target these membrane proteins.

But a lack of technology has hampered scientists' efforts to capture key information about these proteins where they live, requiring the use of artificial chemical environments.

In an important breakthrough, scientists at the Yale Nanobiology Institute have decoded a chemical signal that allows them to capture these biological interactions directly from their natural habitat.

The finding, published in *Nature Methods*, opens up new avenues for understanding downstream cellular applications in human health.

"The traditional way to analyze these membrane proteins was to put them into an artificial environment, but that was a lot like studying a fish out of water," said Kallol Gupta, assistant professor of cell biology and lead author of the study.

Previous experiments relied on the "brute force" energy of conventional mass spectrometry techniques to remove proteins from their greasy membrane environments. But this damaged the proteins and their ability to bind with other molecules—including, crucially, those of potential therapeutic value.

The team at Yale's West Campus identified a class of chemicals, called superchargers, that worked to gently destabilize the membrane while leaving the embedded proteins intact. They were then able to show how cell membranes regulate the speed of neurotransmitter release, a key step in central nervous system signaling.

This breakthrough technology opens the way for scientists to screen future therapeutics precisely and directly at the point where proteins encounter new drugs.

Aniruddha Panda, a postdoctoral researcher in the Gupta Lab, was the first author of the study, which included collaborators at the Rothman Lab, Yale Nanobiology Institute, the University of Oxford, Aarhus University, Texas Tech University and Sorbonne Université. Alongside an in-house mass spectrometer, the authors also utilized the West Campus Analytical Core and the Imaging Core in their experiments.

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