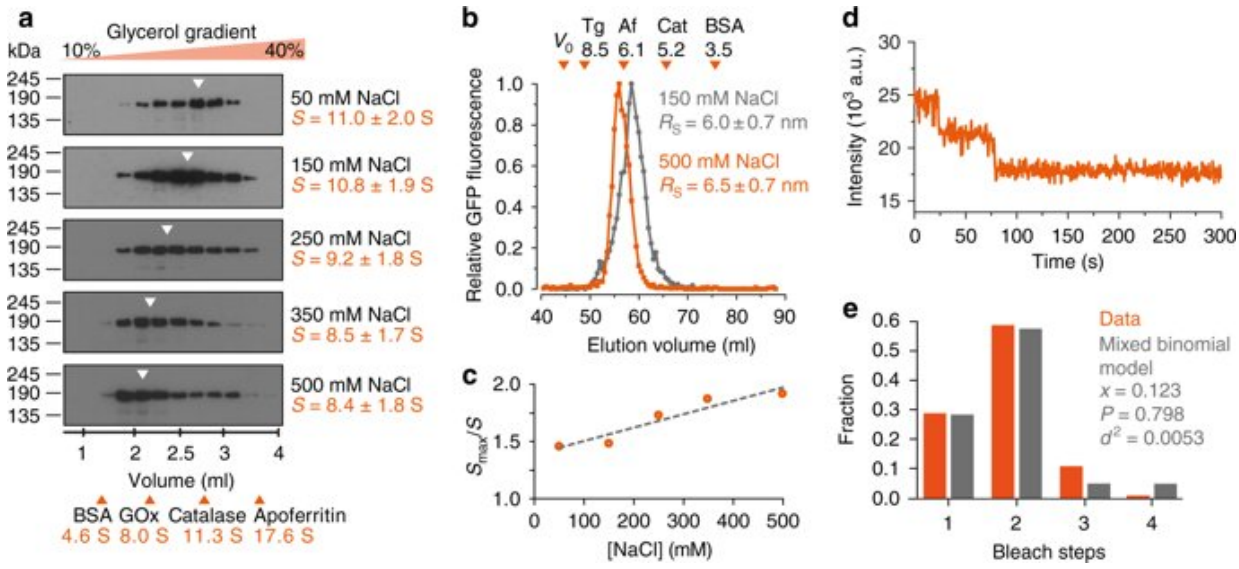
Marathon-running molecule could speed up the race for new neurological treatments

July 12 2019, by Peter Thorley



KIF1C is a dimer. a Fractions from glycerol gradients of KIF1C-GFP at different salt concentrations as indicated. Elution peaks of standard proteins are indicated with orange arrowheads. GOx, glucose oxidase. Errors are SEM. Uncropped gels are provided in Source Data file. b Size exclusion chromatography of KIF1C-GFP at 150 mM NaCl (grey) and 500 mM NaCl (orange). Elution peaks of standard proteins (Tg thyroglobulin, Af apoferritin, Cat catalase, BSA bovine serum albumin) and void volume V0 are indicated by orange arrowheads. Errors are SEM. c Frictional coefficient of KIF1C-GFP at different salt concentrations indicating that KIF1C elongates with increasing ionic strength. d, e Bleach curve of KIF1C-GFP on microtubules showing discrete steps in fluorescent decay in d. Experimentally determined bleach steps are shown in e together with best fit to a mixed binomial model of dimers and tetramers with x being the fraction of tetramer and p the fraction of active GFP molecules. n=108 motors. Data are provided in Source Data file Credit: PTPN21

and Hook3 relieve KIF1C autoinhibition and activate intracellular transport, Nature Communications. DOI: 10.1038/s41467-019-10644-9

Scientists at the University of Warwick have discovered a new process that sets the fastest molecular motor on its marathon-like runs through our neurons.

The findings, now published in *Nature Communications*, paves the way towards new treatments for certain neurological disorders.

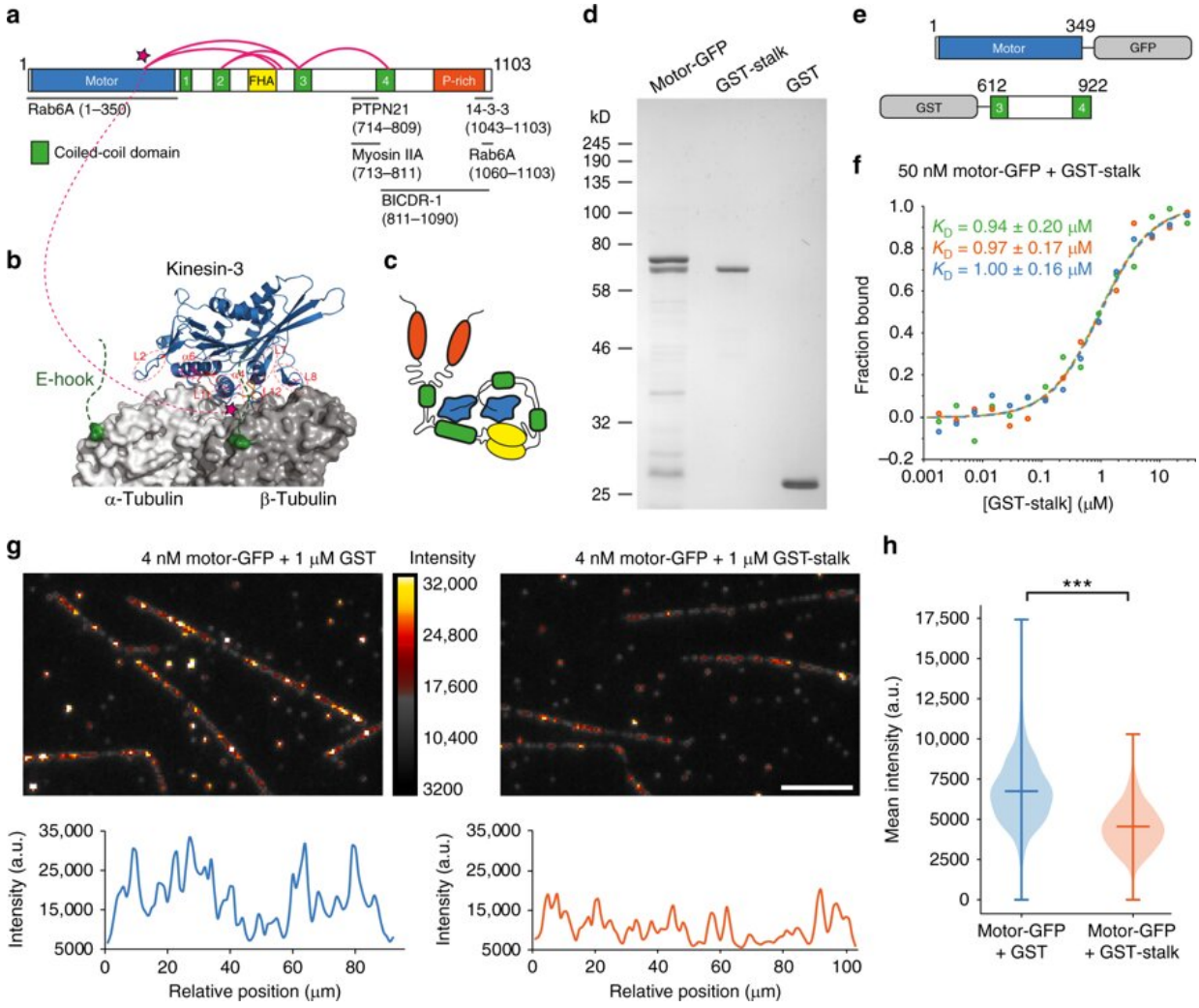
The research focuses on KIF1C: a tiny protein-based molecular motor that moves along microscopic tubular tracks (called microtubules) within neurons. The motor converts chemical energy into mechanical energy used to transport various cargoes along microtubule tracks, which is necessary for maintaining proper neurological function.

Neurons are cells that form the basis of our nervous system, conducting the vital function of transferring signals between the brain, the spinal cord and the rest of the body. They consist of a soma, dendrites, and an axon, a long projection from the cell that transports signals to other neurons.

Molecular motors need to be inactive and park until their cargo is loaded onto them. Neurons are an unusually long (up to 3 feet) type of nerve cell, and because of this marathon distance, these tiny molecular motors need to keep going until their cargo is delivered at the end.

Insufficient cargo transport is a crucial cause for some debilitating neurological disorders. Faulty KIF1C molecular motors cause hereditary spastic paraplegia, which affects an estimated 135,000 people worldwide. Other studies have also found links between defective

molecular motors and neurological disorders such as Alzheimer's disease and dementia.



KIF1C is autoinhibited by intramolecular interactions of stalk and motor domain. a Schematic primary structure of KIF1C with motor domain (blue), coiled-coil domains (green), FHA domain (yellow), and Proline-rich domain (orange). Crosslinks identified using mass spectrometry after treatment with BS3 or EDC are shown as magenta loops. Published binding sites for KIF1C interactors are indicated below. See Figs. S2 and S3 for ion fragmentation of crosslinked peptides. b Motor domain of related KIF1A on tubulin. The region in the motor domain that interacts with KIF1C stalk is indicated by magenta stars. c

Hypothetical model of autoinhibited KIF1C conformation based on identified crosslinks. d Coomassie-stained SDS-PAGE gel of purified KIF1C motor domain, stalk domain and GST control. e Schematic primary structure of KIF1C motor and stalk proteins used here. f Binding affinity measurements and Kd model fits from three microscale thermophoresis experiments probing the interaction of KIF1C motor domain with the stalk domain. g Representative TIRF images showing microtubule decoration of KIF1C motor domain in the presence of GST (control) and KIF1C tail domain. Scale bar 5 µm. Linescans of one of the microtubules from each field is shown below. h Quantification of mean intensity of KIF1C motor domain on microtubules. Distribution is shown together with mean and full extent of data. n = 690 and 659 microtubules, respectively, pooled from six experiments. Credit: PTPN21 and Hook3 relieve KIF1C autoinhibition and activate intracellular transport, Nature Communications. DOI: 10.1038/s41467-019-10644-9

The research shows how, when not loaded with cargo, KIF1C prevents itself from attaching to microtubule tracks by folding on to itself. The scientists also identified two proteins: PTNPN21 and Hook3, which can attach to the KIF1C molecular motor. These proteins unfold KIF1C, activating it and allowing the motor to attach and run along the microtubule tracks—like firing the starting pistol for the marathon race.

The newly identified activators of KIF1C may stimulate cargo transport within the defective nerve cells of patients with hereditary spastic paraplegia, a possibility the team is currently exploring.

Commenting on the future impact of this research, Dr. Anne Straube from Warwick Medical School said: "If we understand how motors are shut off and on, we may be able to design cellular transport machines with altered properties. These could potentially be transferred into patients with defect cellular transport to compensate for the defects. Alternatively they can be used for nanotechnology to build new materials

by exploiting their ability to concentrate enzymes or chemical reagents. We are also studying the properties of the motors with patient mutations to understand why they function less well.

"We still know very little about how motors are regulated. There are 45 kinesins expressed in human cells, but we only have an idea how the motors are activated for less than a handful of them. KIF1C is the fastest motor in neurons and the motor that is the most versatile—it delivers cargoes efficiently to all processes in a neuron, not just the axon."

More information: Nida Siddiqui et al. PTPN21 and Hook3 relieve KIF1C autoinhibition and activate intracellular transport, *Nature Communications* (2019). DOI: 10.1038/s41467-019-10644-9

Provided by University of Warwick