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Are Microtubules a Key to Understanding Nerve Degeneration during Gulf War Illness?

Soldiers serving in the first Gulf War – Neurological Disorders that are difficult to diagnose, including twice the frequency of ALS

Pesticides

Drugs to protect against nerve agents

Botulinium toxin vaccine

Other ??

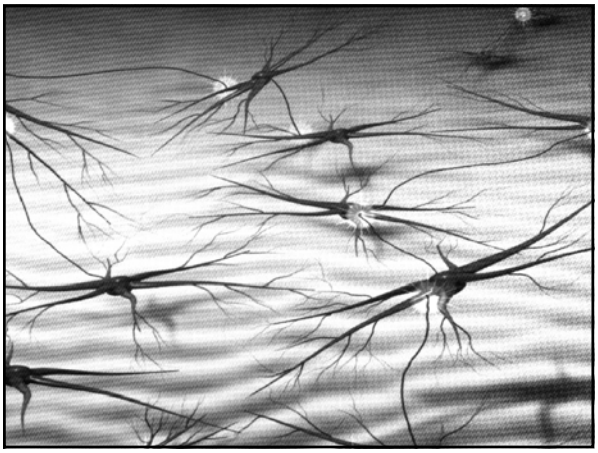
The Nervous System

Made up of nerves that extend from the brain and spinal cord

Neurodegenerative Diseases

ALS
Alzheimer's disease
Hereditary Spastic Paraplegia
Parkinson's disease
Huntington's disease
Many others

What causes them, and what can we do to treat them?



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East Lansing, Michigan

Temple University School of Medicine, Philadelphia, PA

University of Wisconsin, Madison, Wisconsin

Drexel University College of Medicine, Philadelphia PA

Delivering on the Promise

A story about one neurodegenerative disease: Hereditary Spastic Paraplegia

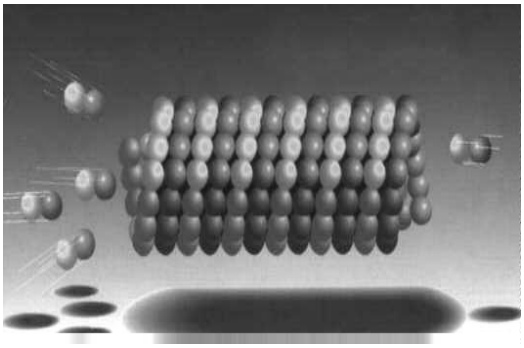
Completely genetic

Degeneration of corticospinal tracts

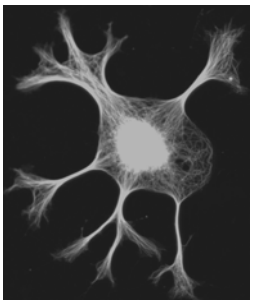
Typically adult onset

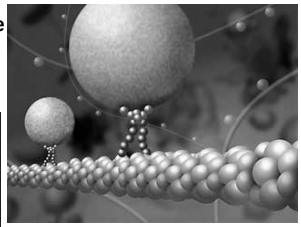
Studies on neurons from lab rats

It's also a story about Microtubules

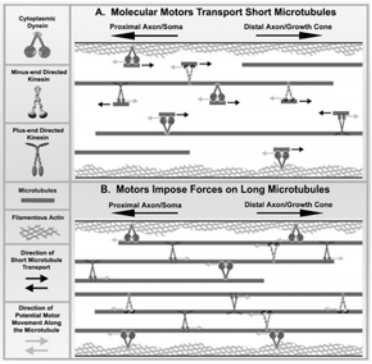


Molecular motors move vesicular organelles along microtubules





But how do the microtubules themselves enter the axon and get organized?



Inside the axon are

Long

and

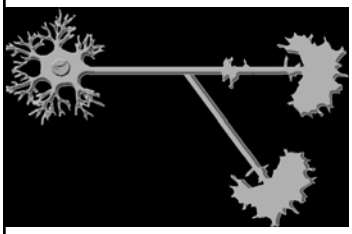
Short

Microtubules

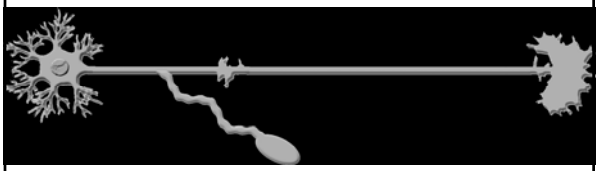
Where do short microtubules come from?

Long ones are chopped.

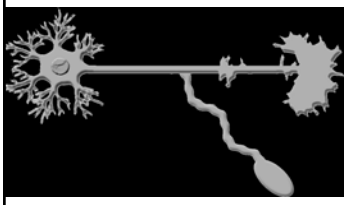
Axogenesis and Branch Formation



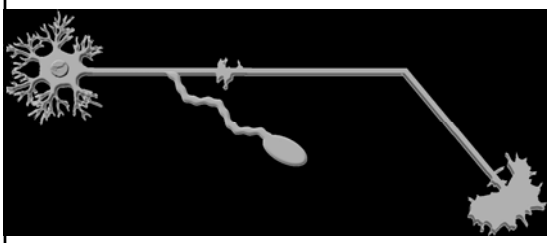
Elongation



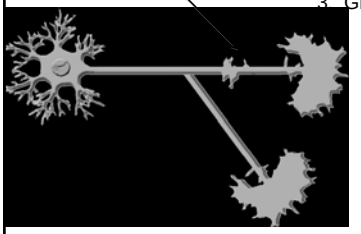
Retraction



Navigation

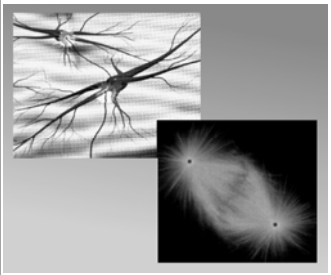


1. Cell Body (centrosome)
2. Site of branch formation
3. Growth Cone



Key sites of microtubule severing

Are Neuronal and Mitotic Microtubules Organized by Similar Mechanisms?



Nucleation proteins
Assembly proteins
Disassembly proteins

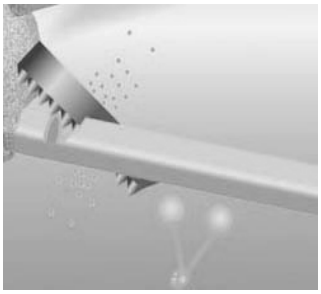
Motor proteins

Bundling proteins

Severing proteins

Crosslinking proteins
Small G-proteins
Other cytoskeletal proteins

Where do short microtubules come from? The Cut and Run Model

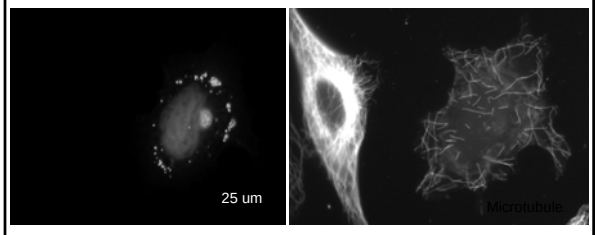


Microtubule-Severing Proteins

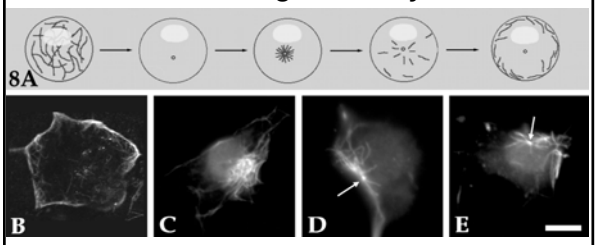
Katanin

AAA ATPase

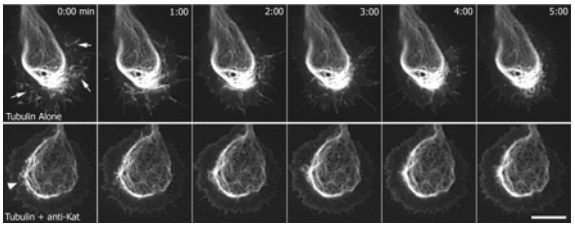
Microtubules are severed into short iieces fibroblasts induced to overexpress katanin



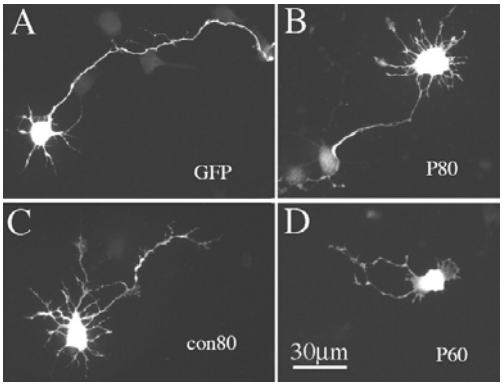
Katanin inhibition with function blocking antibody



Katanin Severs Microtubules in the Growth Cone



Overexpression of katanin doesn't increase axonal branching



Hereditary Spastic Paraplegia

Table 1. Genetic classification of hereditary spastic paraplegia (HSP).

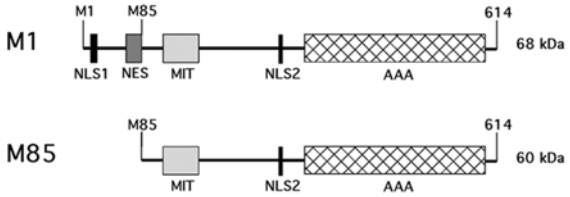
Genome database designation	Chromosome	Inheritance	Phenotype	Genetic defect
SPG1	Xq28	X-linked	Complicated	L1CAM
SPG2	Xq22	X-linked	Both	PLP
SPG3*	14q11.2-24.3	AD	Pure	Unknown
SGP4	2p22-21	AD	Both	Spastin
SPG5	8p12-q13	AR	Pure	Unknown
SPG6	15q11.1	AD	Pure	Unknown
SPG7	16q24.3	AR	Both	Paraplegin
SPG8	8q24	AD	Pure	Unknown
SPG9*	10q23.3-24.2	AD	Complicated	Unknown
SPG10	12q13	AD	Pure	Unknown
SPG11	15q13-15	AR	Both	Unknown

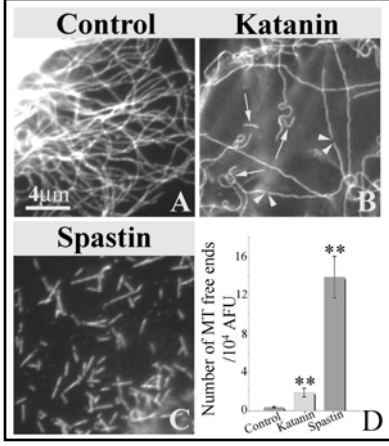
* Types of HSP with overlapping clinical features with Machado-Joseph disease.

Caused by mutations to various genes.

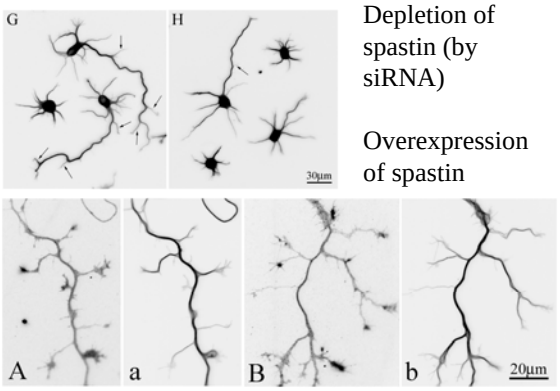
The most common gene encodes for a protein called SPASTIN

Spastin:
another protein with microtubule-severing properties (Elena Rugarli)





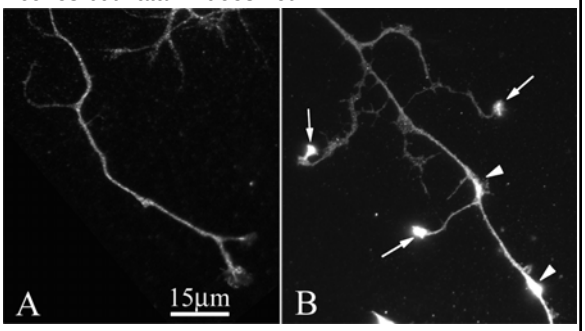
Katanin and spastin overexpression produce different patterns of microtubule severing

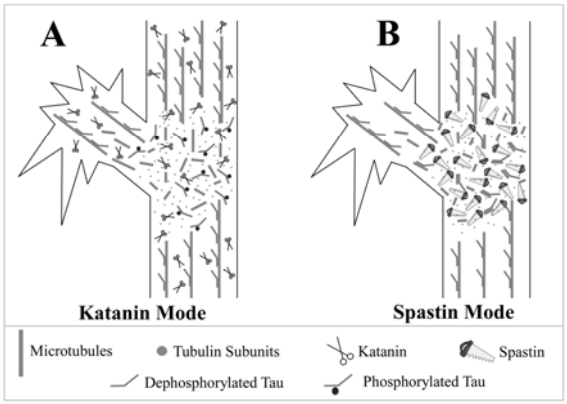


Depletion of spastin (by siRNA)

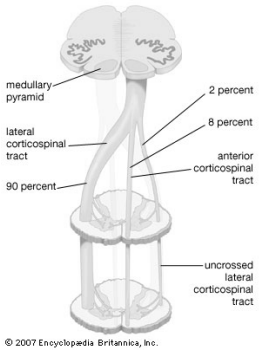
Overexpression of spastin

Spastin concentrates at branch points and growth cones but katanin does not





What about HSP?



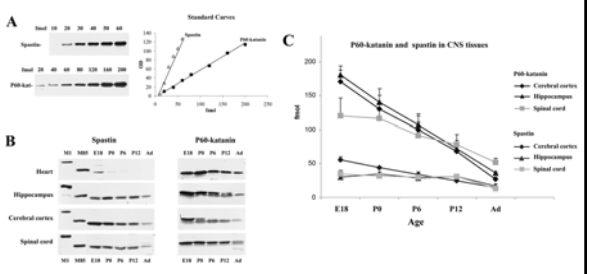
Hereditary Spastic Paraplegia:

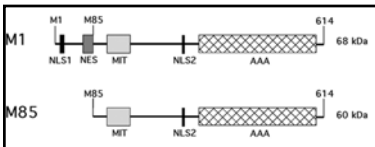
Autosomal dominant mutations to spastin gene

Degeneration of corticospinal tracts in adult

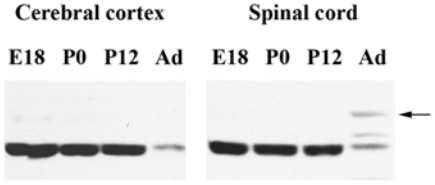
-No developmental problems
-No problems in PNS or in most other regions of CNS

"Loss of function" scenario?



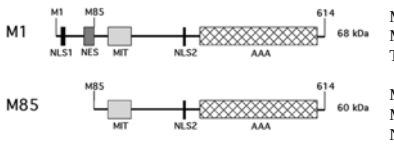


Does "gain of function" make more sense?



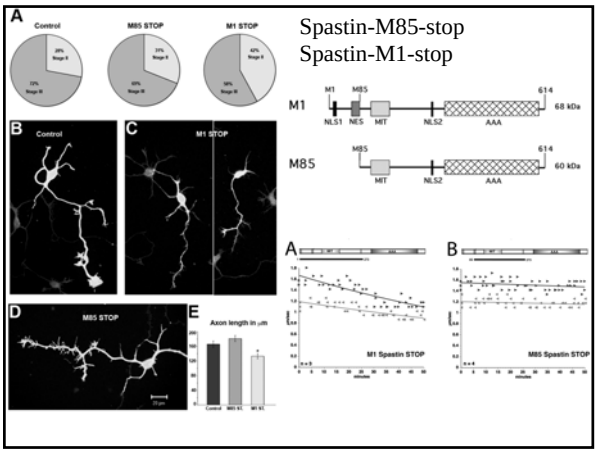
ONLY adult spinal cord contains M1

Our Theory:



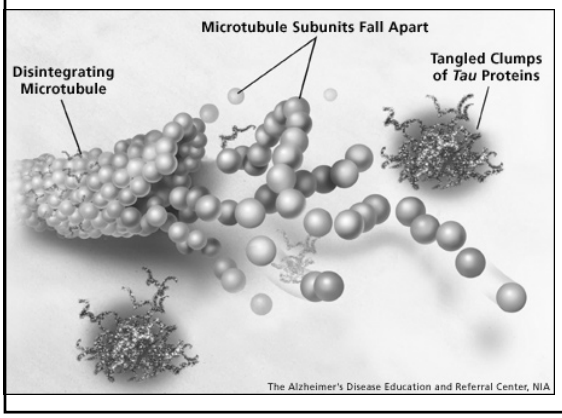
M1
Mutant
Toxic

M85
Mutant
Not Toxic

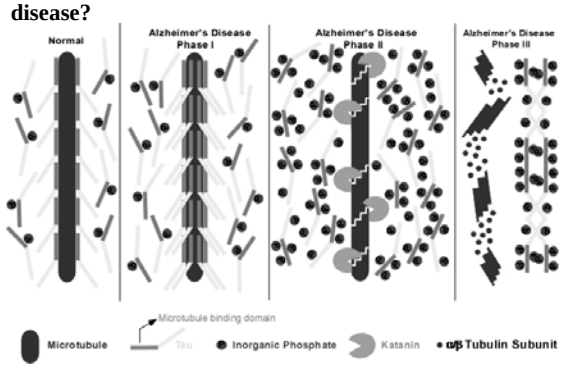


Spastin-M85-stop
Spastin-M1-stop

What about Alzheimer's Disease ?

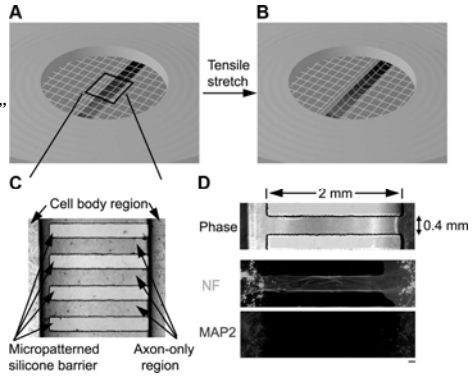


Too much microtubule-severing in Alzheimer's disease?



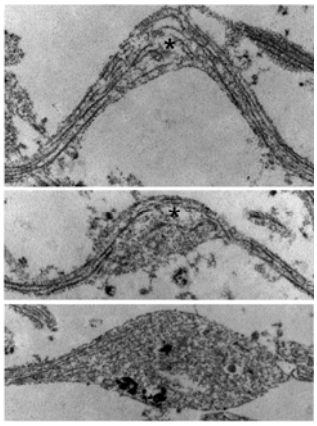
How about injury?

Axons get "whiplashed" in TBI

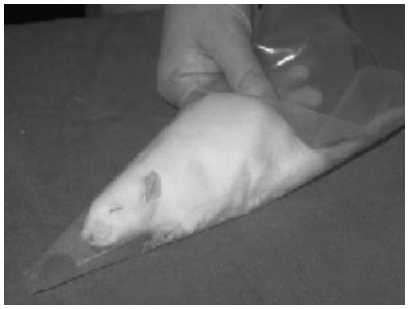


Stretch causes microtubules to break-

Are microtubules a "weak link" in the axon?



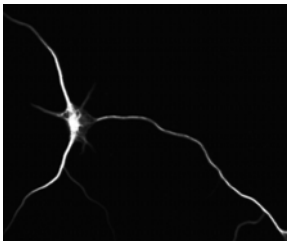
Model for Gulf War Illness: Expose lab rat to same toxins as soldiers



Plus stress by restraint

Now we can study what's going wrong with the microtubules in the nerves

Conclusions



- The "cut and run" model for axonal microtubules
- Central for axonal development and relevant to robust health of adult neurons
- Understanding what goes wrong in various diseases and injuries is dependent upon intimate knowledge of what happens with the microtubules

Why does all this matter to our veterans?

Prevention

Rapid Response

Therapy

CREDITS

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