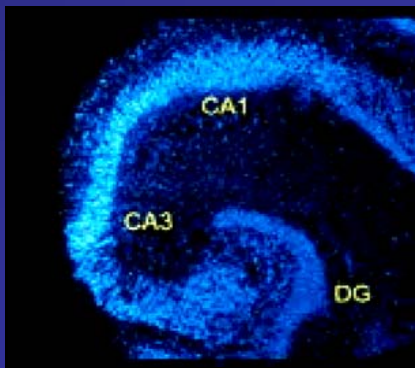


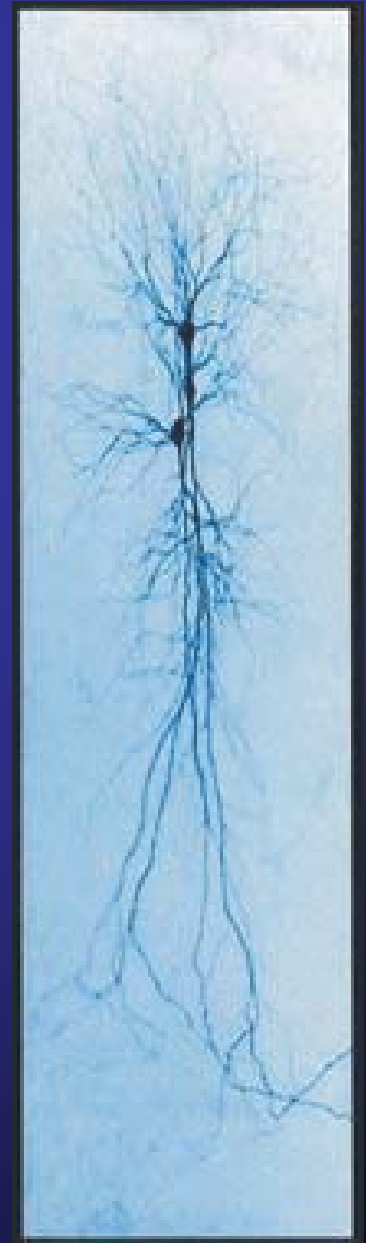
Hormetic immune signaling ... initiates neurological preventative health

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D.M. White, and P.E. Kunkler

The University of Chicago



**The Annual Meeting of the
International Hormesis Society**
April 28-29, 2009,
University of Massachusetts at
Amherst



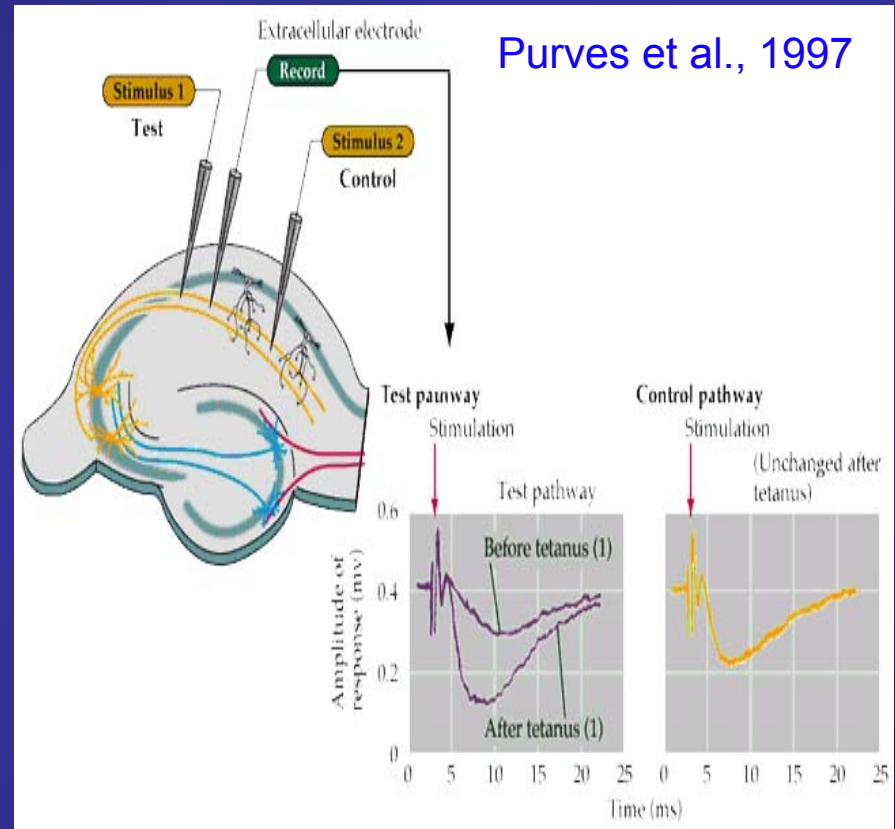
What is Neurological Preventative Health?

- Evidence shows ...
 - ↑Brain activity before the onset of disease
Results in ↓ injury after disease begins
- Involves ...
 - Hebbian synaptic plasticity and its extension
 - Environmental enrichment

Hebbian synaptic plasticity (i.e., learning)

👉 LTP (long-term potentiation) ...

- “Spike” amplitude -
- Involves pre ...
- & post synaptic Δ s
- Seen *in vivo*
- Model of learning

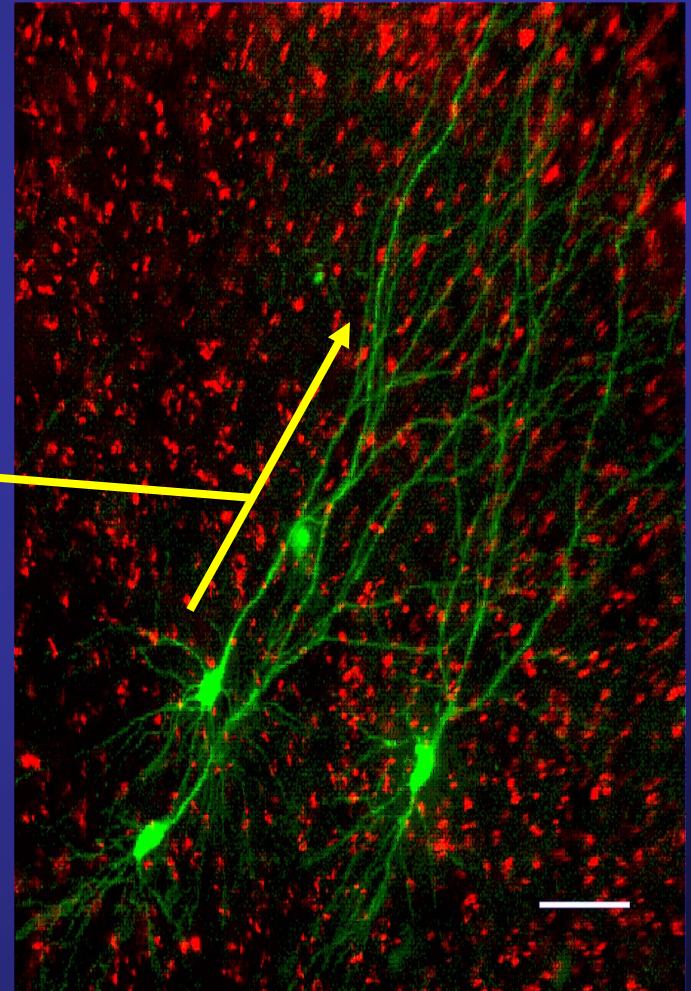


- Including sufficient depolarization ...
 - & back-propagating action potentials (BPAPs)

Microglia & learning

- Neurons (green)
- Activate microglia (red)
- Via BPAPs?
- To enhance learning

Kunkler PE et al., J Neuroscience, 2005
Ziv Y et. al., Nat Neuroscience, 2006



Environmental enrichment (EE)

- ↑ Opportunities for ...
 - Volitional social, intellectual & physical activity
- Protective against ...
 - Epilepsy, Stroke, Alzheimer's,
 - and Parkinson's diseases
 - Aging ... *Mattson*



Young et al., Nat Med, 1999

How does EE-neuroprotection occur?

- ↑ Brain activity
- Triggers microglial activation and ...
 - Irritative, low-level immune signaling and
 - Resultant interactive adaptive responses
- Thus, brain too is governed by ...
 - “If it doesn’t kill you, it makes you stronger”

Utility of environment enrichment research

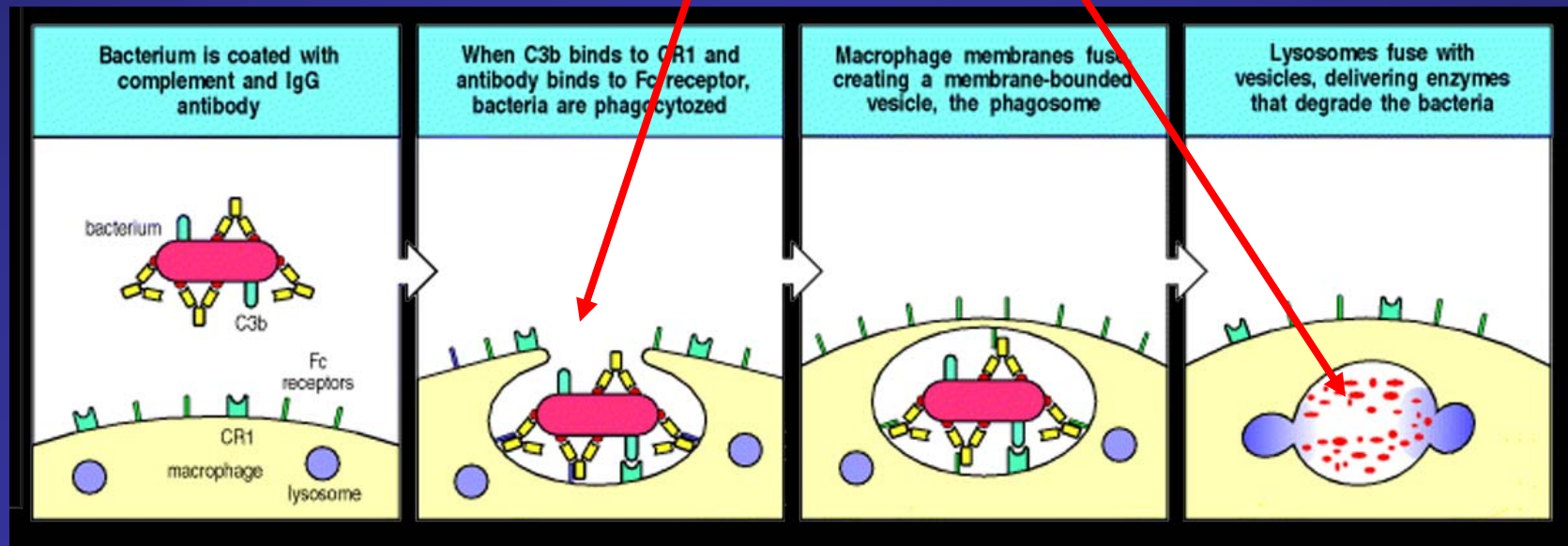
- Genetic propensity to disease
 - Not always the case that ...
 - 1 gene → 1 protein → 1 disease (“genetic determinism”)
 - Instead, ...
 - experience (or environment) can modify disease severity
- Understanding basic mechanisms ...
 - Establish rationale for patient care - empowerment
 - Lead to new treatment strategies
 - Based on “Mother Nature’s” signaling
 - Would be more effective with fewer negative effects

Immune signaling & brain

- Pro-inflammatory signaling
 - Increasingly evident with normal brain function
 - And not just with disease
- Malenka - TNF- α & excitability (\uparrow AMPA, \downarrow GABA)
- Schatz - MHC expression & synaptic plasticity
- We began exploring ...
 - How monomeric IgG, TNF- α , & microglial activation
 - Initiate signaling of neuroprotection

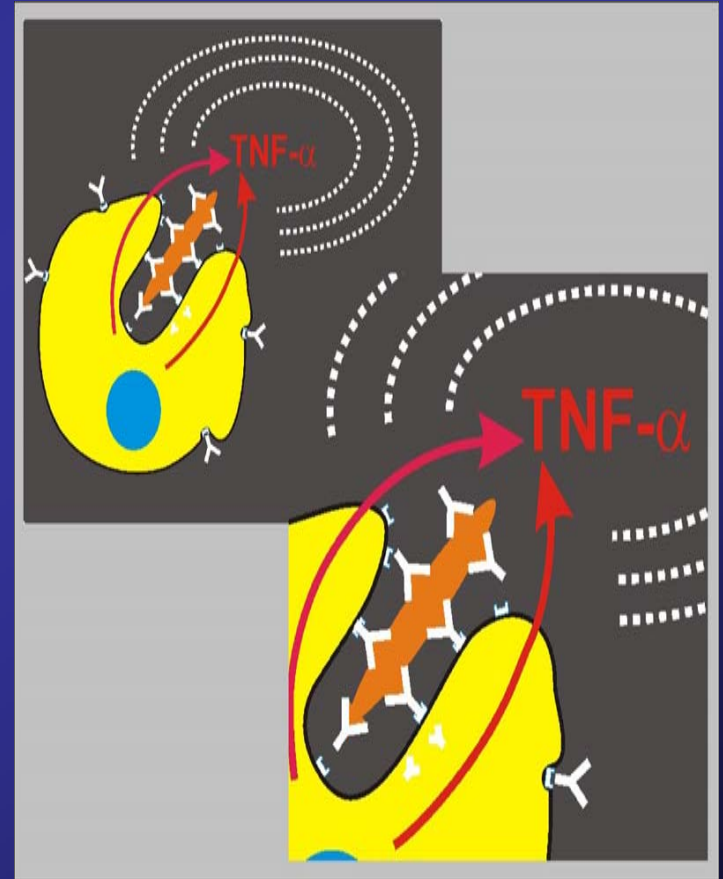
With disease, IgG and TNF- α destroy foreign microbes

- IgG mostly consider with disease
- Via formation of immune complexes that
- Help microglia engulf & destroy microbes



Destruction occurs via phagocytosis & toxic TNF- α

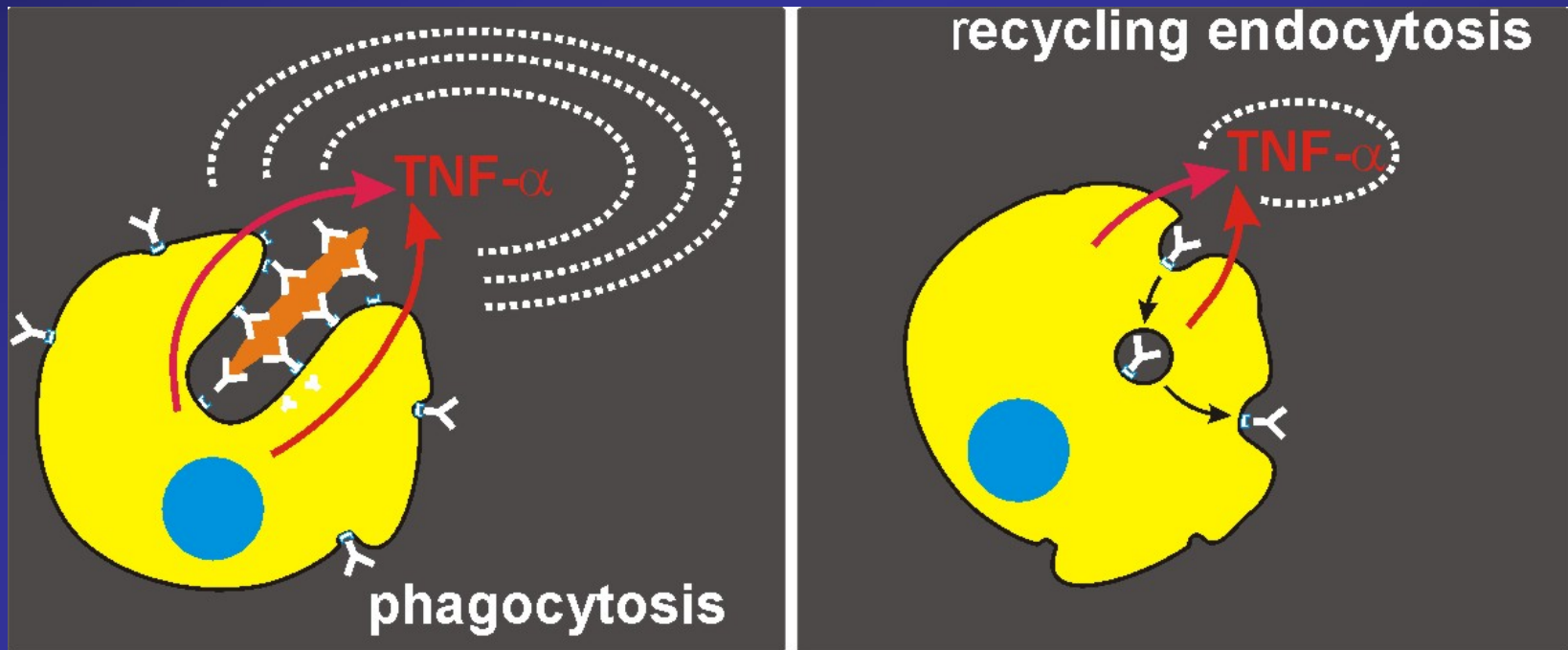
- Phagocytosis involves
 - Lysosome formation
 - That digests microbe
 - Using ...
 - immune complexes
- And releases
 - toxic levels of TNF- α
 - At cusps



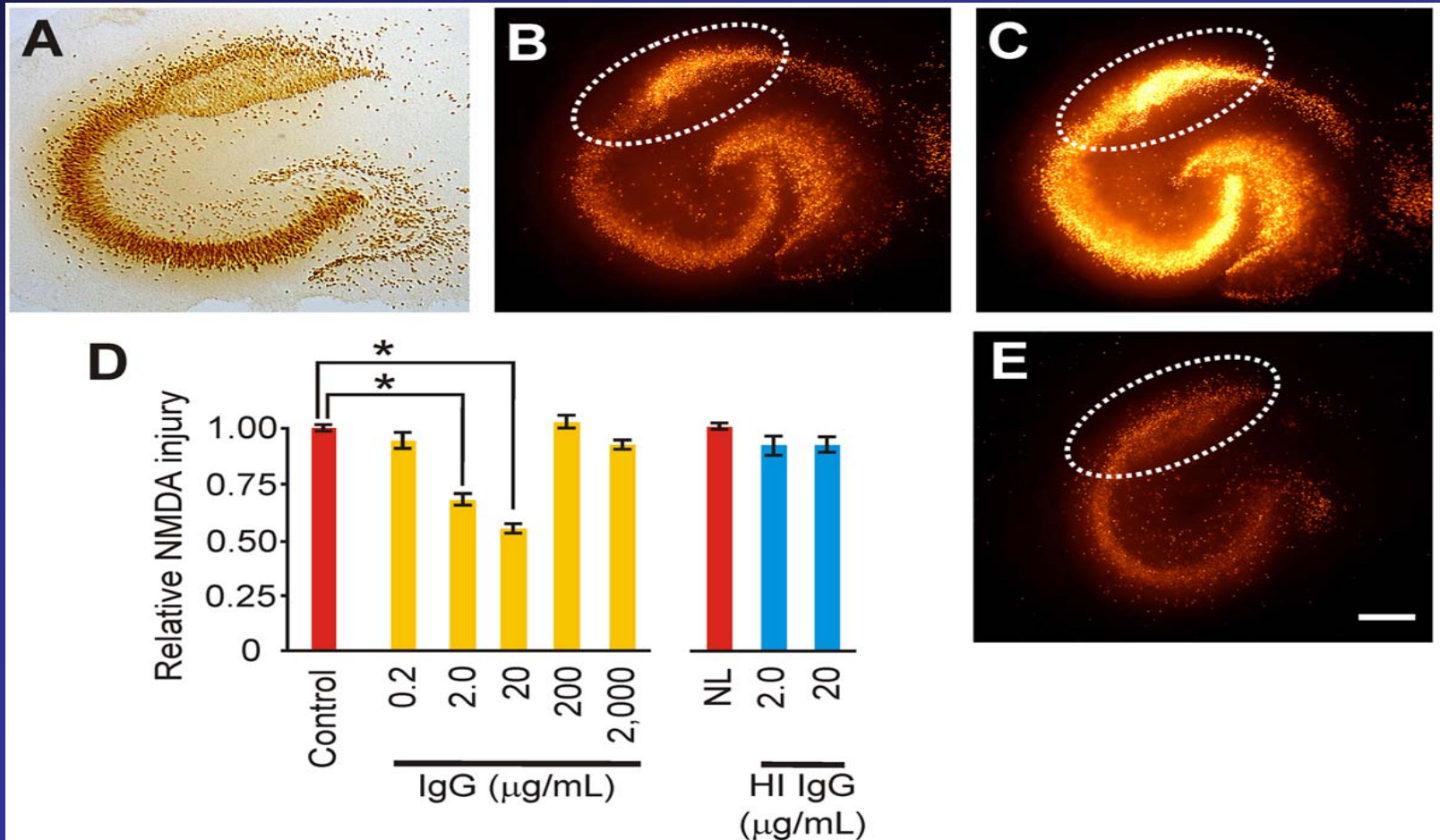
Murray RZ et al., Science, 2005

Monomeric IgG also has signaling function in normal brain

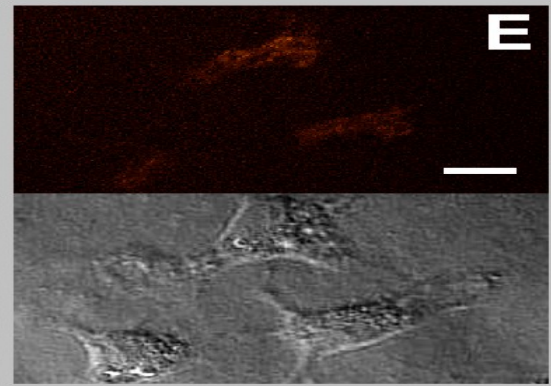
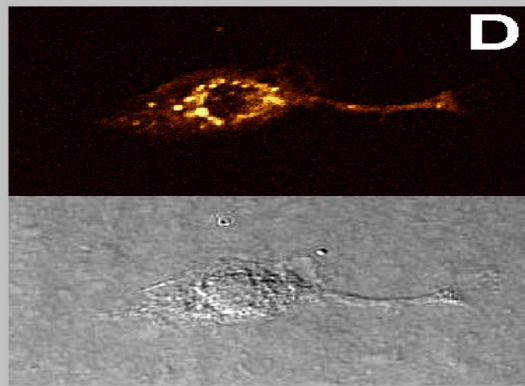
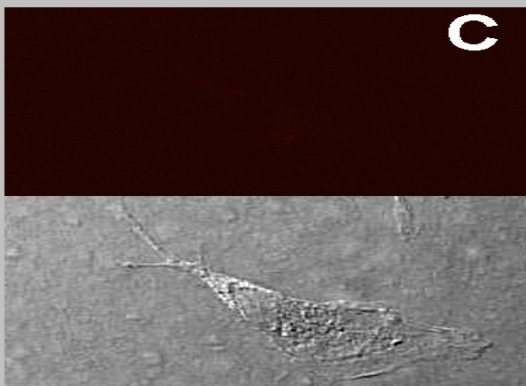
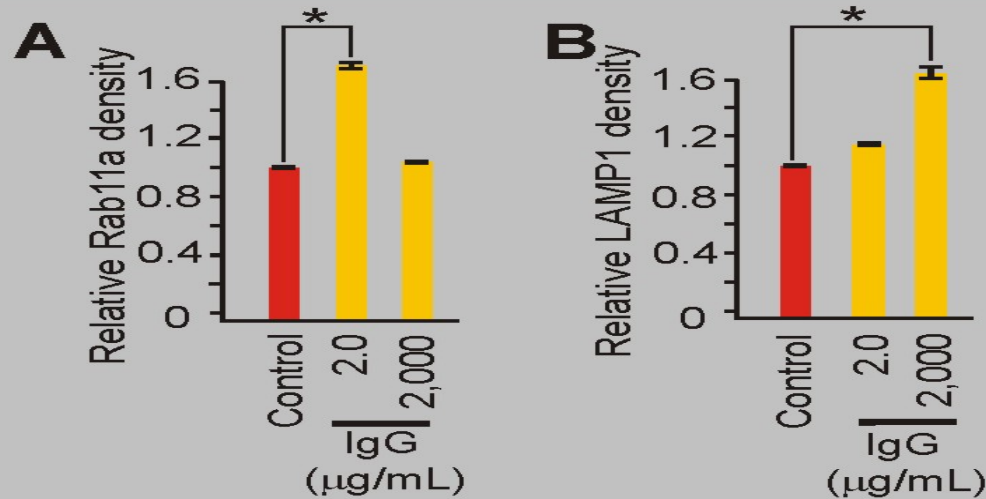
- Via recycling endocytosis & TNF- α , not phagocytosis, involving microglia



Physiological IgG levels protect brain after days but not acutely

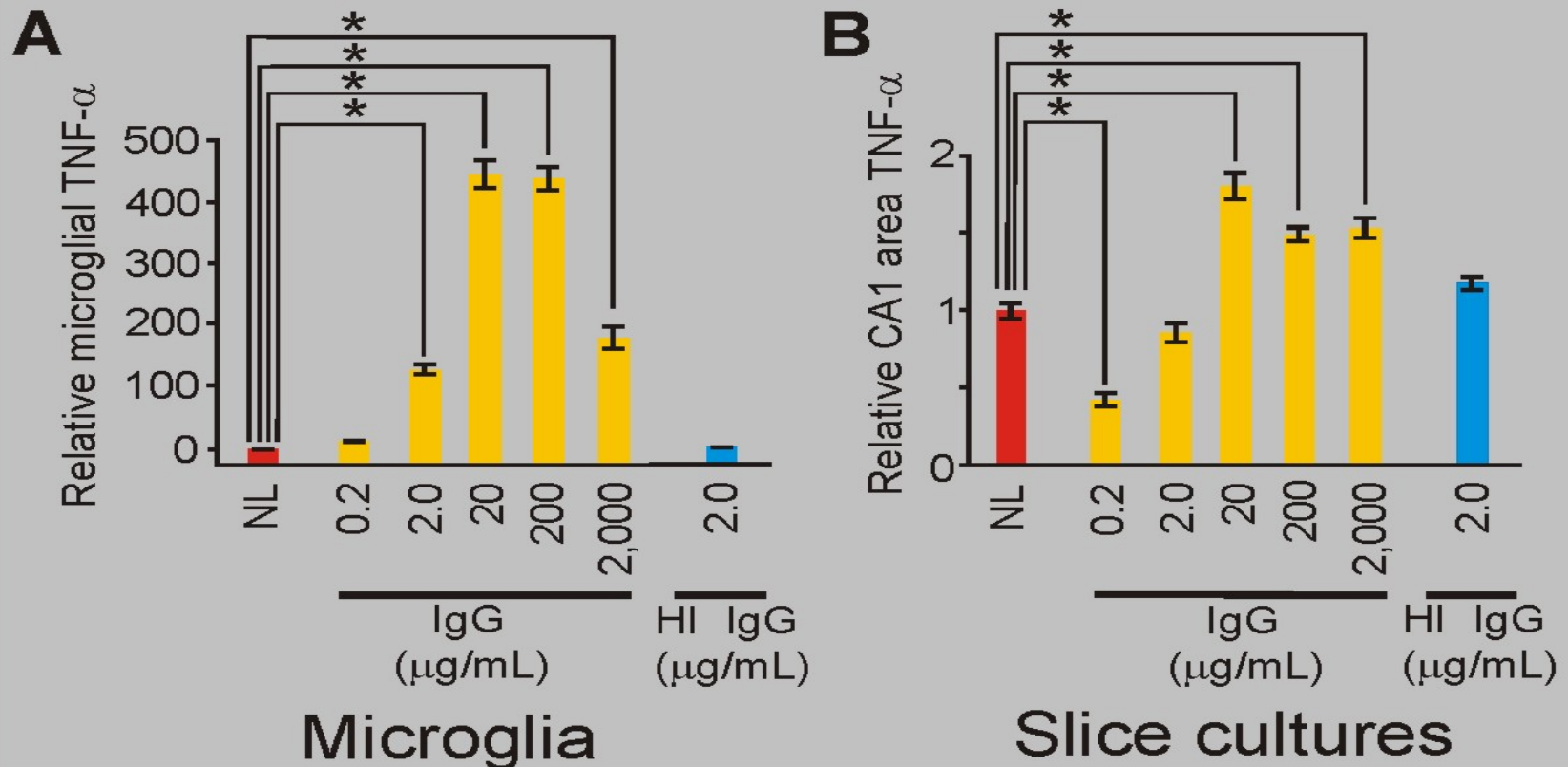


Physiological IgG \uparrow microglial recycling endocytosis

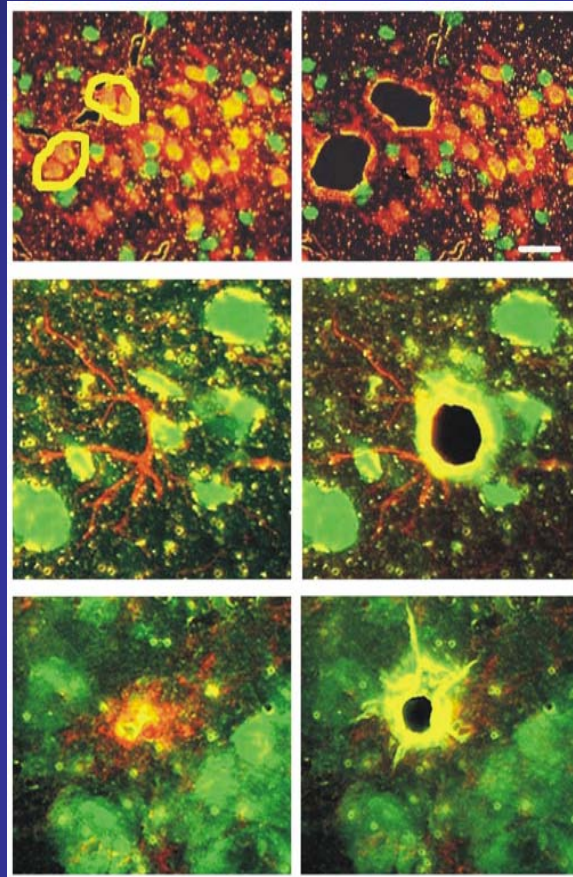
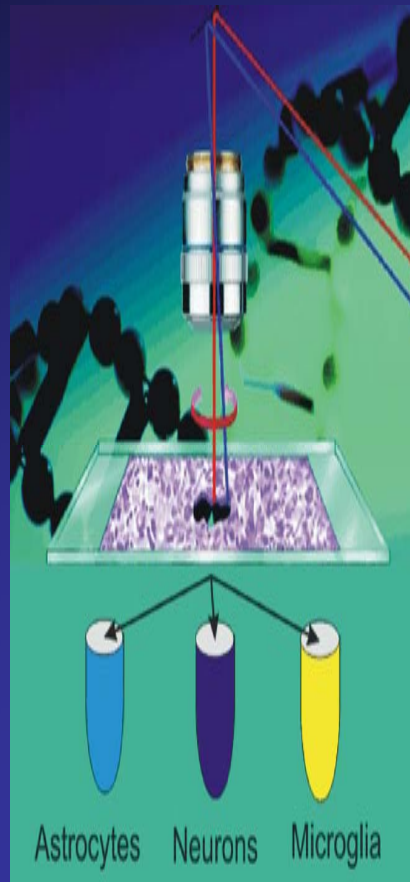


Physiological IgG \uparrow TNF- α

- IgG triggers hormetic TNF- α Δ s

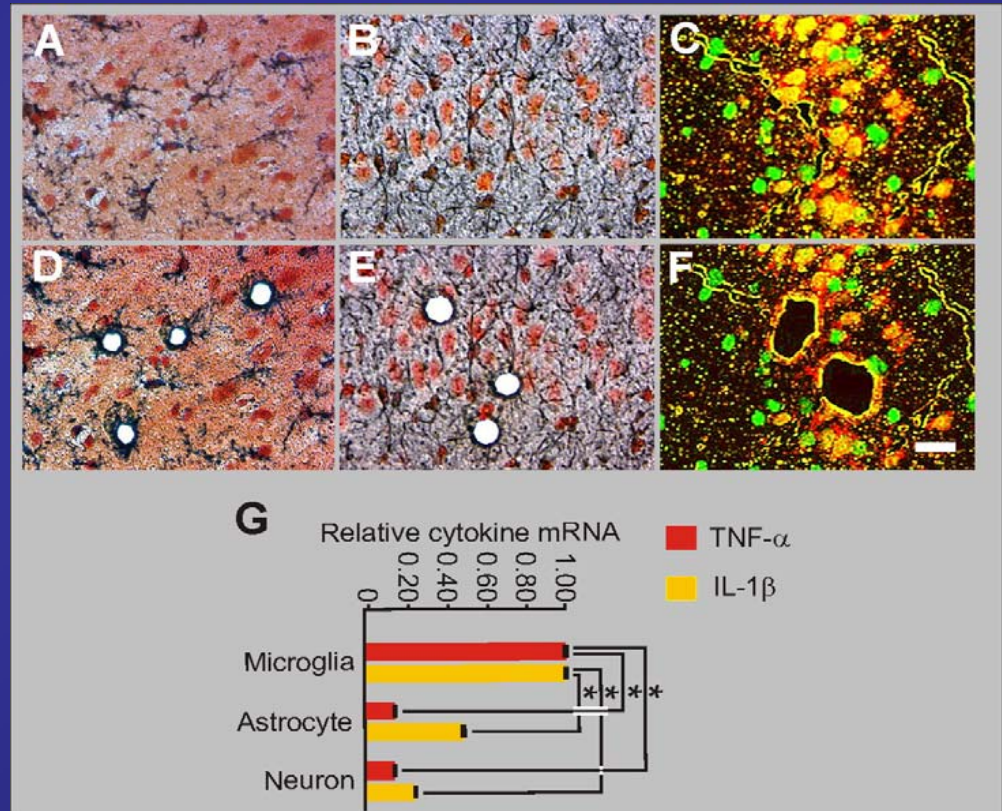


Laser dissection microscopy used to identify cellular cytokine mRNA origin



TNF- α comes from microglia

- Slices exposed to spreading depression
 - Activate microglia
 - Immune cells
 - Generate TNF- α
- Learning similar
 - \uparrow TNF- α
 - Microglia
- Both protect
 - Via TNF- α

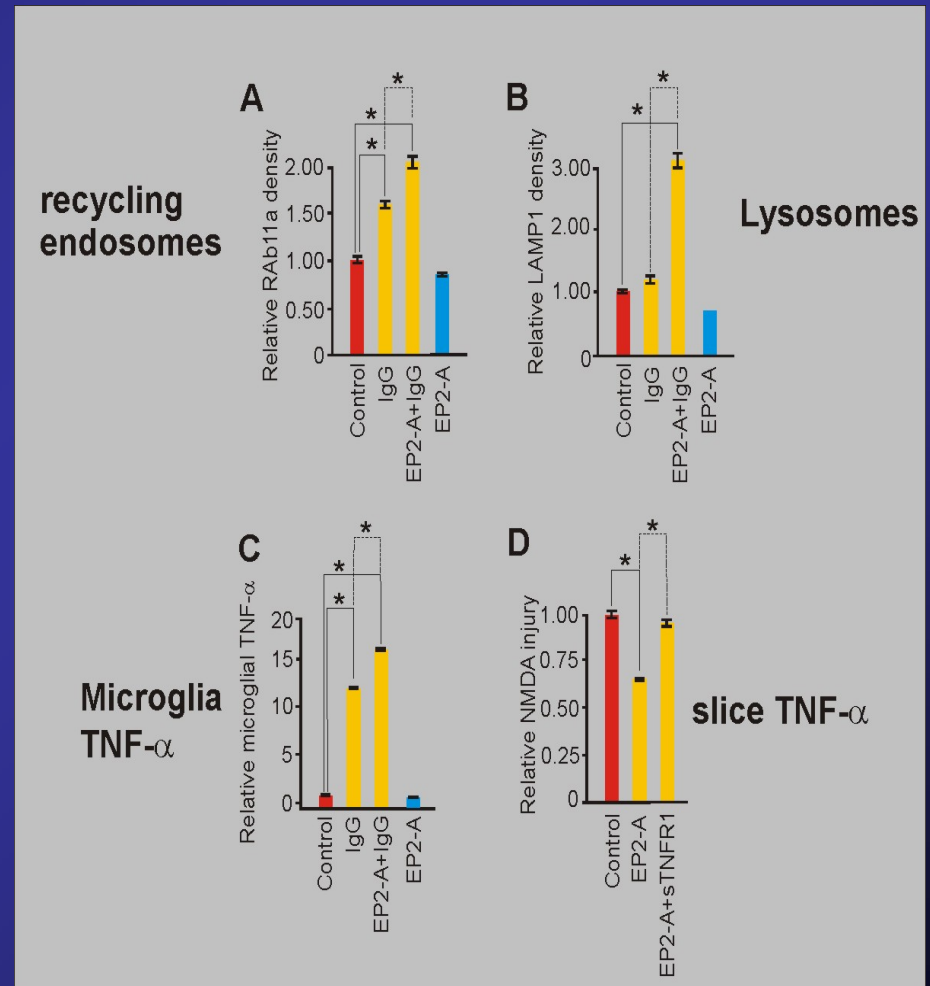


Microglial inhibition by minocycline

- Acts as an anti-inflammatory agent
 - After the onset of disease
 - Where it is neuroprotective
- But before disease onset
 - It prevents neuroprotection from IgG
 - And microglial \uparrow TNF- α & \uparrow recycling endocytosis
- Adding support to the notion that ...
 - Low-level, irritant pro-inflammatory cytokine signaling
 - Initiates neuroprotective changes over time

In contrast, eicosanoids amplify IgG-based effects

- Eicosanoids ...
 - ↑ neuronal activity
 - ↑ endocytosis MØ
- Microglia?
 - ↑ IgG effects
 - ↑ endocytosis
 - ↑ TNF- α
 - ↑ (EP2) protection



SUMMARY

- Monomeric IgG
 - Not just for immune complex Rx's & disease
- Signals in normal brain ~ to activity
 - To increase recycling endocytosis
 - And TNF- α production of activated microglia
- Cytokines alter genes/proteins to INITIATE
 - Downstream, adaptive changes of ...
 - Growth factors
 - ROS system signaling
 - Glucose metabolism
- With the latter responsible for EVOKING
 - Activity-dependent neuroprotection

Conclusions

- Brain & immune signaling
 - Closely interrelated
 - Traditionally examined with disease
 - & high-level, acute toxic changes
 - But

Conclusions

- Brain uses these same immune systems...
 - Involving
 - Peripheral & central
 - And innate & adaptive immunity
 - To evoke low-level, chronic irritative signals
 - Which INITIATE
 - Adaptive Δ s that EVOKE the protection