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STERILE INFLAMMATION

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STERILE INFLAMMATION groups

- Autoimmune diseases
- Systemic inflammatory conditions
  - Osteochondrosis
  - Arteriosclerosis
- Catastrophic events
  - Trauma (inclusive surgery)
  - Vascular occlusion
- Unresolved immune actions
  - Cancer (some forms)
  - Glomerulonephritis
  - Endometriosis
  - Posttraumatic residual inflammation
  - Spinal pain – tendinitis – other nociceptive and neuropathic pain

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STERILE INFLAMMATION unresolved immune actions (2)

- **Neuroinflammatory diseases**
  - Parkinson
  - Amyotrophic Lateral Sclerosis
  - Alzheimer disease
  - Cerebellar degeneration
- **Inflammatory psychiatric disorders**
  - Major Depressive Disorder (MDD)
  - Schizophrenia
  - Bipolar disorder
  - Autism
  - ADHD
  - Posttraumatic stress disorder
  - Emotional stress
- **Ophthalmological diseases**
  - Age related Macular Degeneration (AMD)

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STERILE INFLAMMATION pathology

- **Cellular level**
  - The transfer of control
  - Oxidative stress
  - The redox equilibrium
  - Epigenetic marks
- **From the periphery to the brain**
  - Nervous pathway
  - Intravascular cytokines
- **From the brain to the innate immune system**
  - The sympathetic nervous system
  - The HPA axis
- **The everlasting battle: the unresolved immune action**

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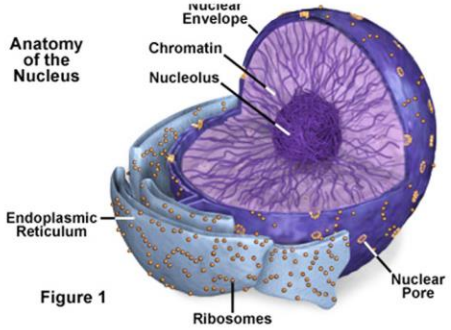
STERILE INFLAMMATION
the initiation of cell stress

GENETIC PART

eIF2a

PHOSPHORYLATION

STRESS



EPIGENETIC PART

energy saving
selective translation only
chaperone proteins
epigenetic memory

TRANSCRIPTION PROGRAM

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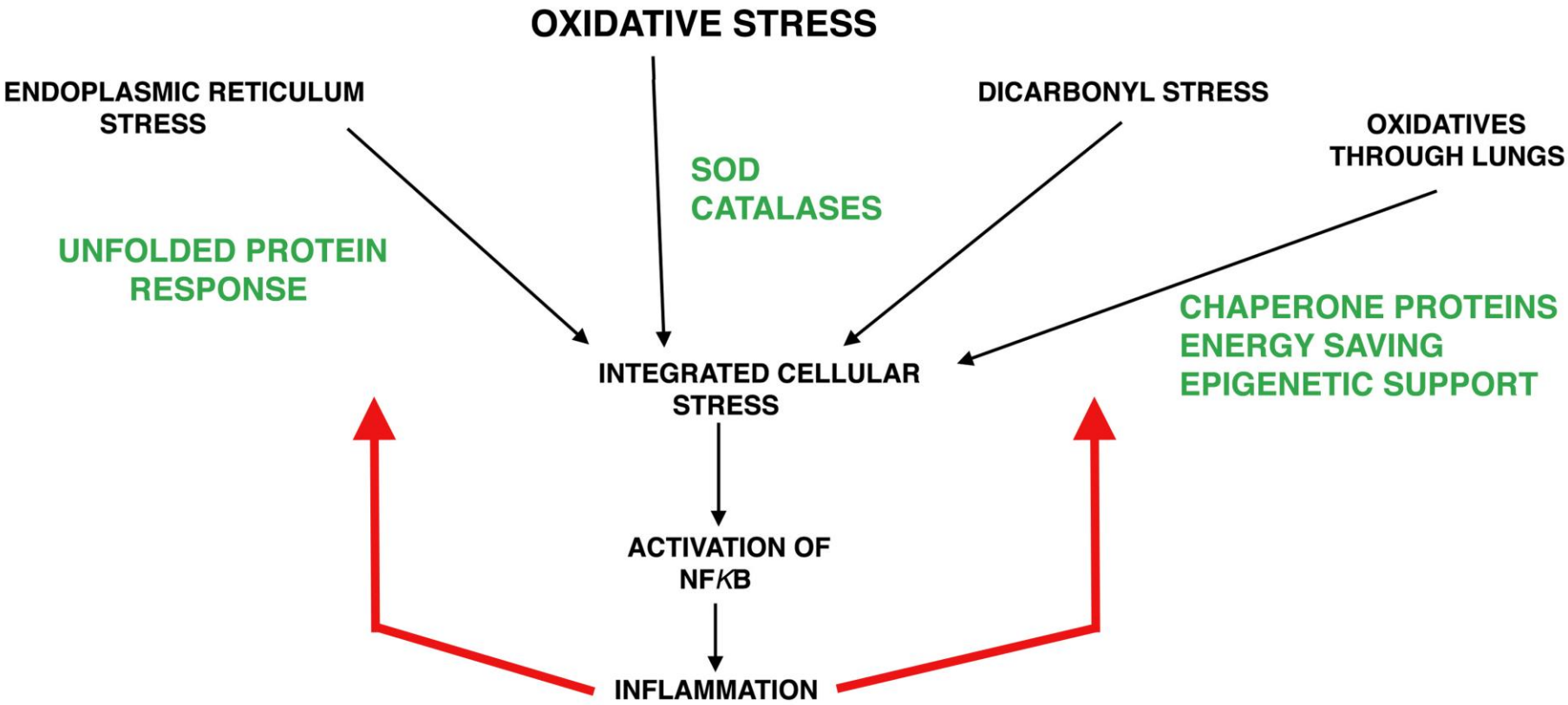
STERILE INFLAMMATION
cellular stress



CELL STRESS

the epigenetic part of chromatin

- **May protect the cell because it knows how to deal with a specific form of stress**
- **Is known to persevere – sometimes – in a response even if the factors causing the response have changed**
- **Epigenetic changes:**
  - **Methylation/demethylation**
  - **Posttranslational histone modifications**
  - **(uncoded) microRNAs**

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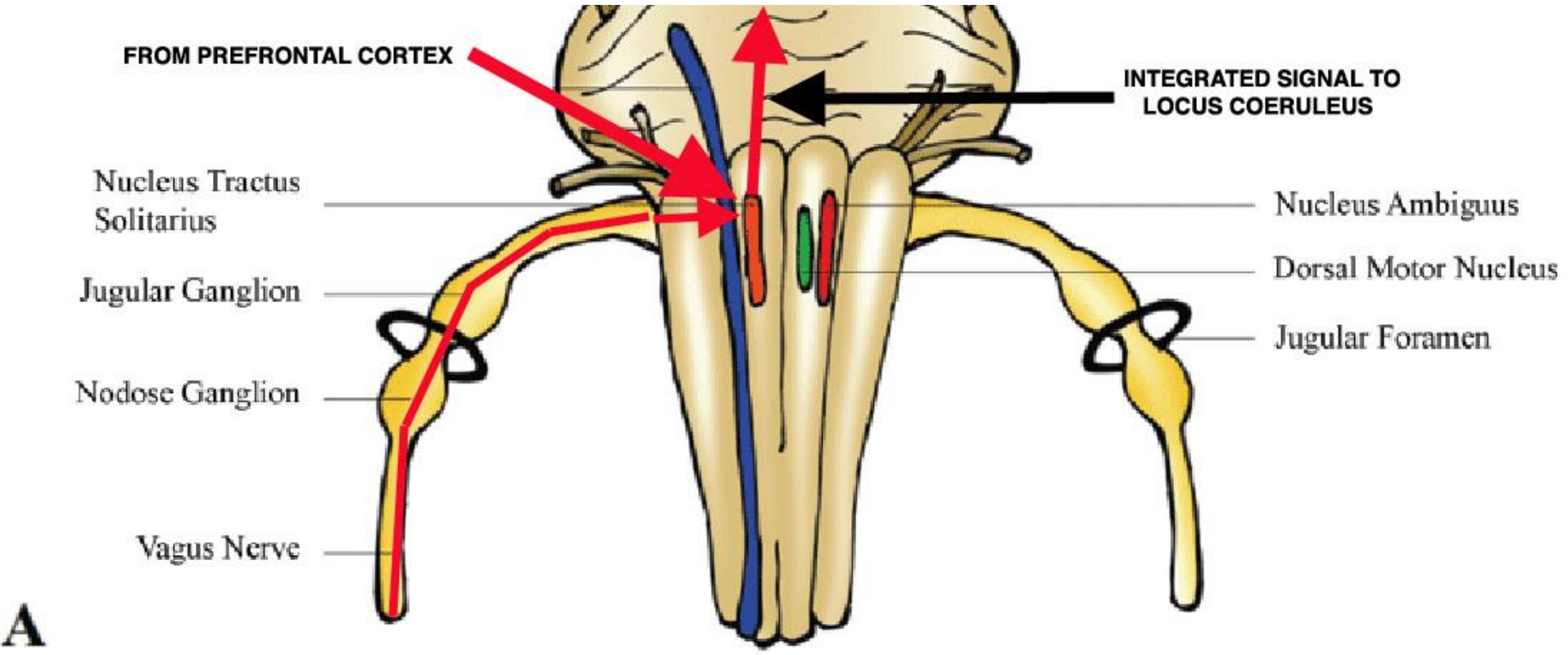
integration of somatic and mental stress in NTS



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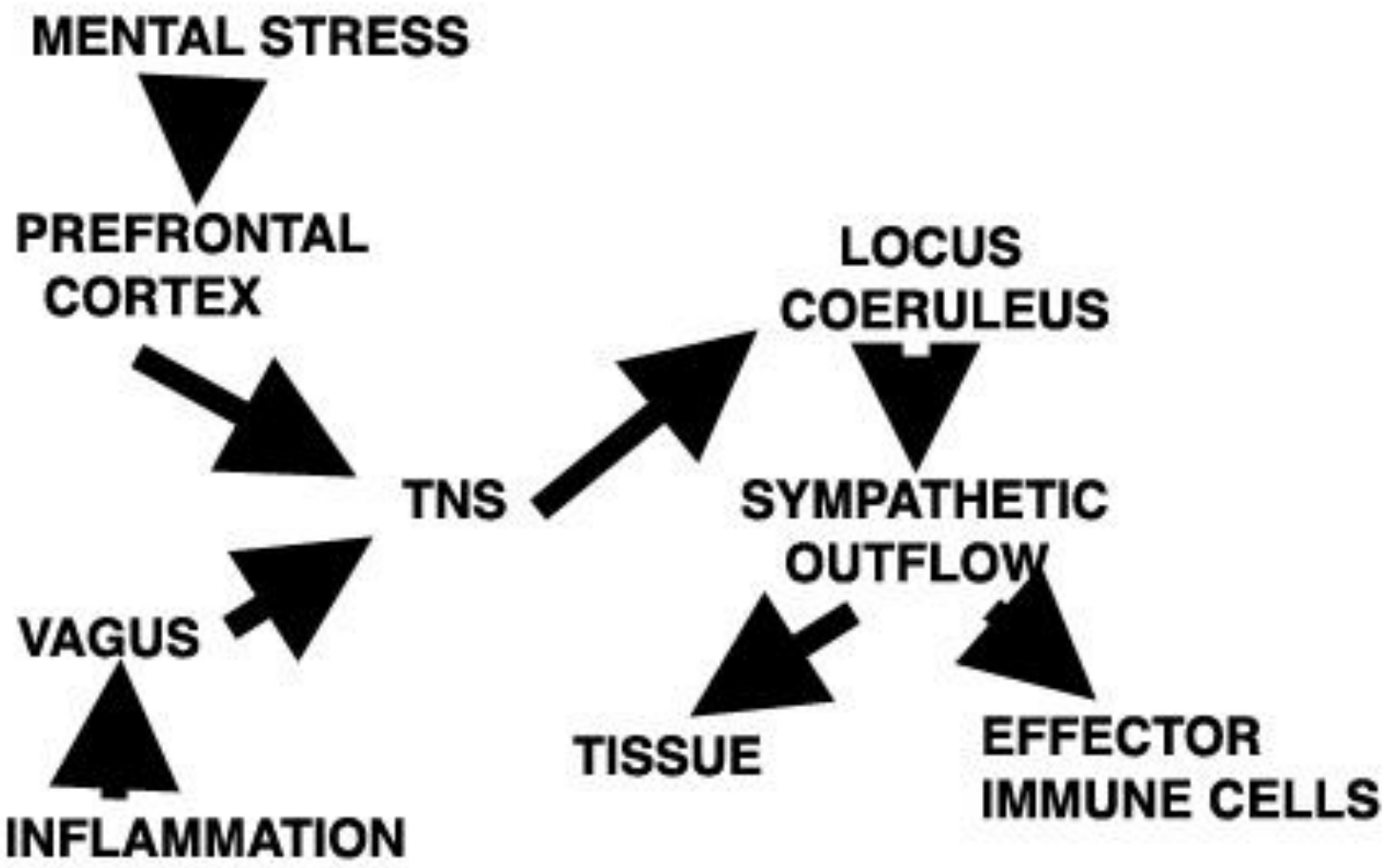
From stress to immune response



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OXIDATIVE STRESS

1990-2000: The period of lament

- Oxidative stress tends to initiating a negative cycle
  - Each destructive action consumes an electron
- chain reactions are common
- Experience with anti-oxidant substances has been disappointing
  - The “anti-oxidant paradox”
- Oxidative stress may therefore cause significant secondary tissue damage
  - Following vascular occlusion
    - Coronary infarction
    - Stroke
    - Intentional vascular occlusion
  - Following trauma
  - Following prolonged inflammation

OXIDATIVE STRESS

- **Counterarguments**
  - **Transfer of electrons is the basis of aerobic life**
  - **Transfer of electrons implies the presence of radicals**
  - **Radicals play a crucial role in intracellular signaling**
    - **Cross talk with Ca^{2+} ions**
    - **Second messengers**
  - **Additionally, nature could not foresee old age**

Albert Szent-Gyorgyi

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2007: INTRAVENOUS PRF

- Based on work by Nordenstrom (1993)
  - Cancer metastases
  - Low intensity DC
  - Using the vascular tree as a postman for E-fields
- Self experiments
  - Iv PRF is uneventful procedure
  - Causes a fall in CRP
  - Causes (?) mood and energy improvement
- No realistic prospects //

redoxPRF

- **PRF**
  - **Eliciting Electric fields in the physiological range**
  - **With a reduced duty load**
  - **Large currents**
  - **Non-invasive**
  - **Choice between general and regional application**
  - **Effective against oxidative stress**
  - **Without any effect on healthy cells**

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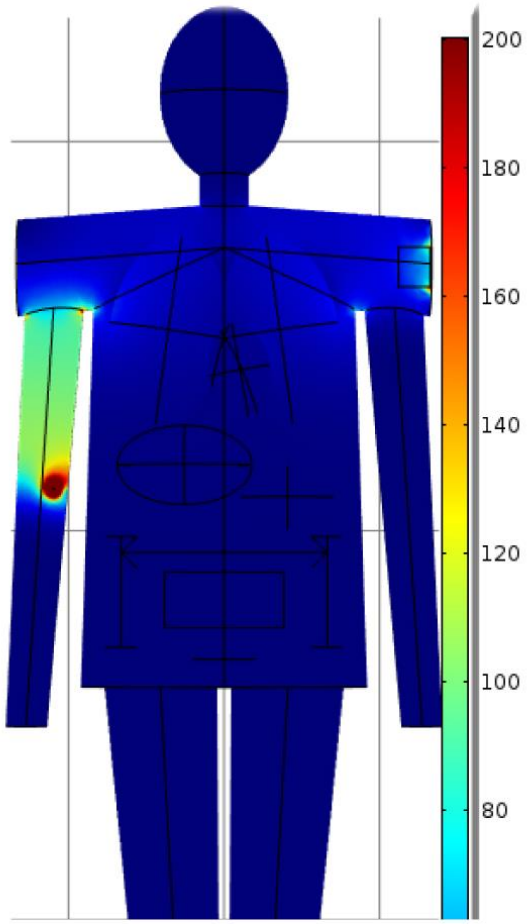
Finite element computer simulation of IV PRF

S.Rampersad, Radboud Medical Center; 2014



0-200 V/m

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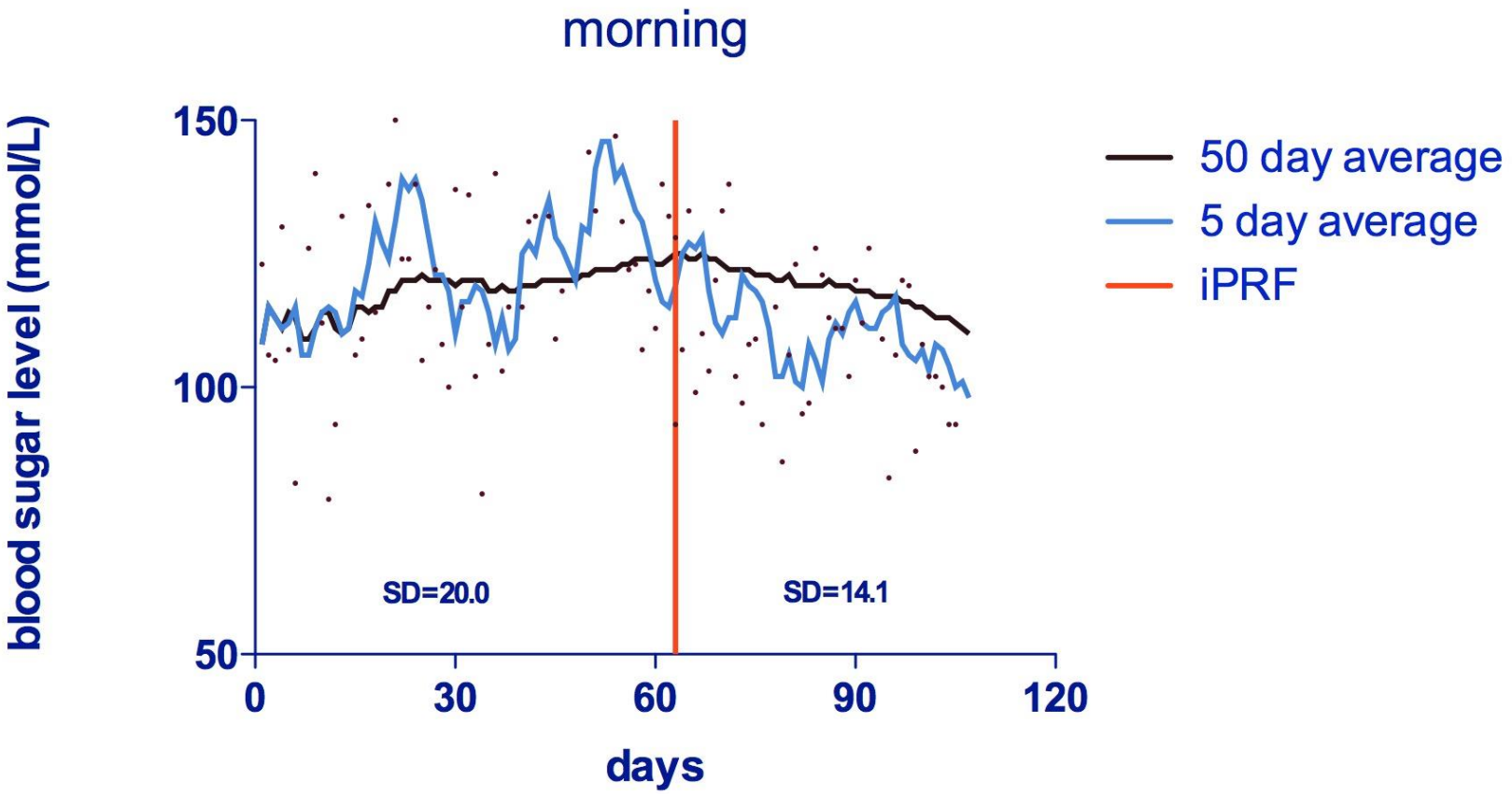
Responses to redoxPRF
observations

- A. A quasi-immediate inflammatory response if antigens or non-self material are present
  - Healing of infected wounds
- B. An attractor switch of the ANS to vagus control
  - Latent period of 12 – 72 hrs
  - Duration up to 2 weeks
- C. A strong anti-inflammatory effect
  - Long duration (1 – 6 months)
  - Persisting trend
- D. Long term: (probably) Epigenetic changes

redoxPRF
effect on diabetes type 2



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redoxPRF

hypothesis on the mode of action

- **A quasi-instantaneous effect on the redox equilibrium of stressed cells**
  - **Physical effect?**
  - **Enzymatic effect?**
- **Secondary effects**
  - **Reduction of oxidative stress**
  - **Reduction of sympathetic outflow**
  - **Correction of the reactivity of effector immune cells**
  - **ANS attractor change to vagal control**
- **Epigenetic change**
  - **Memory of the optimal response**
  - **Prolonging the effect of treatment**

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redoxPRF is NOT stimulation

- **Stimulation**
  - **Elicits a cell response**
  - **Has no memory**

- **redoxPRF**
  - **Does not elicit a cell response**
    - **Basic frequency of RF >> physiological limit**
  - **Effect is memorized as an epigenetic mark**

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RedoxPRF

indications: factors to consider

- **Technical issues**
  - General vs local
  - Interval between treatments should be commensurate to pathology
- **Plasticity of the target structure**
  - Lung: good prospects, long intervals will probably suffice
  - Neuroinflammatory diseases: no plasticity. Lost neurons are not replaced
- **Pathology of the cause of cell stress**
- **Availability**
  - redoxPRF is not (yet) a take home device such as TENS

RedoxPRF
indications

- **Acute inflammatory situations**
  - **Vascular occlusion**
  - **Multitrauma?**
- **Chronic inflammation**
  - **If target has plasticity**
  - **Inflammaging?**
- **Post infection syndromes**
  - **Lyme disease**
  - **Mononucleosis**
  - **Psychiatric inflammatory conditions?**

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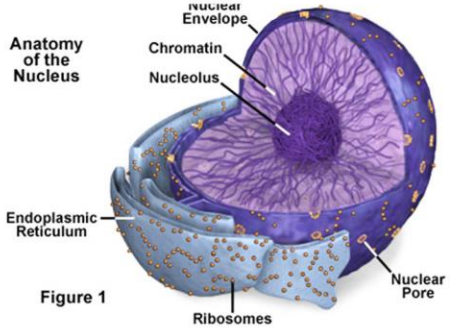

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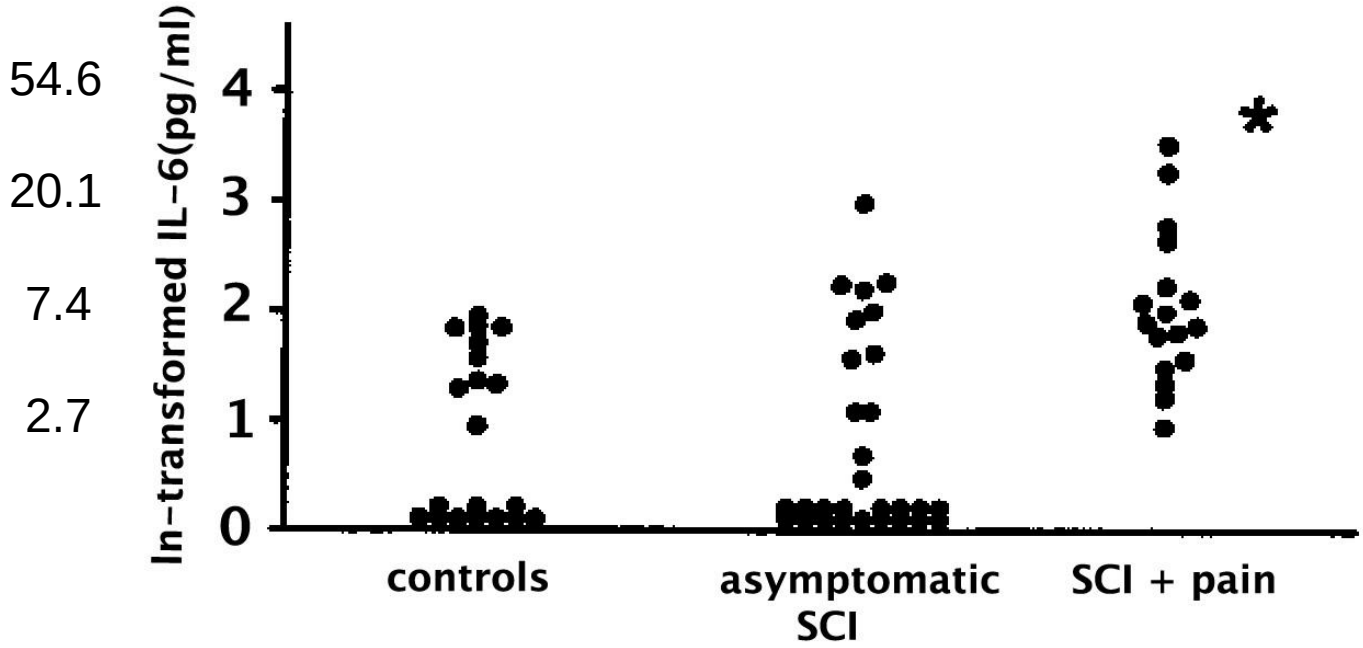
SPINAL CORD INJURY

IL-6 levels vs symptomatology



from:

Clinical Correlates of Elevated Serum Concentrations of Cytokines and Autoantibodies in Patients With Spinal Cord Injury

Andrew L. Davies, MSc, Keith C. Hayes, PhD, Gregory A. Dekaban, PhD

Arch Phys Med Rehabil 2007;88:1384-93.