Anesthesia, Pain, Surgery and Immune Responses

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Talking Points

- Introduction
- Review of Immune System Basics
- Perioperative Sources of Stress:
  - Psychological Stress
  - Surgical Stress (Pain, Hemodynamic and Temperature Effects, Hyperglycemia, Inflammation) and Immune Modulation
  - Anesthetic Agents and Immune Function
  - Opioids, Pain, and Immune Function
- Clinical Implications

Introduction

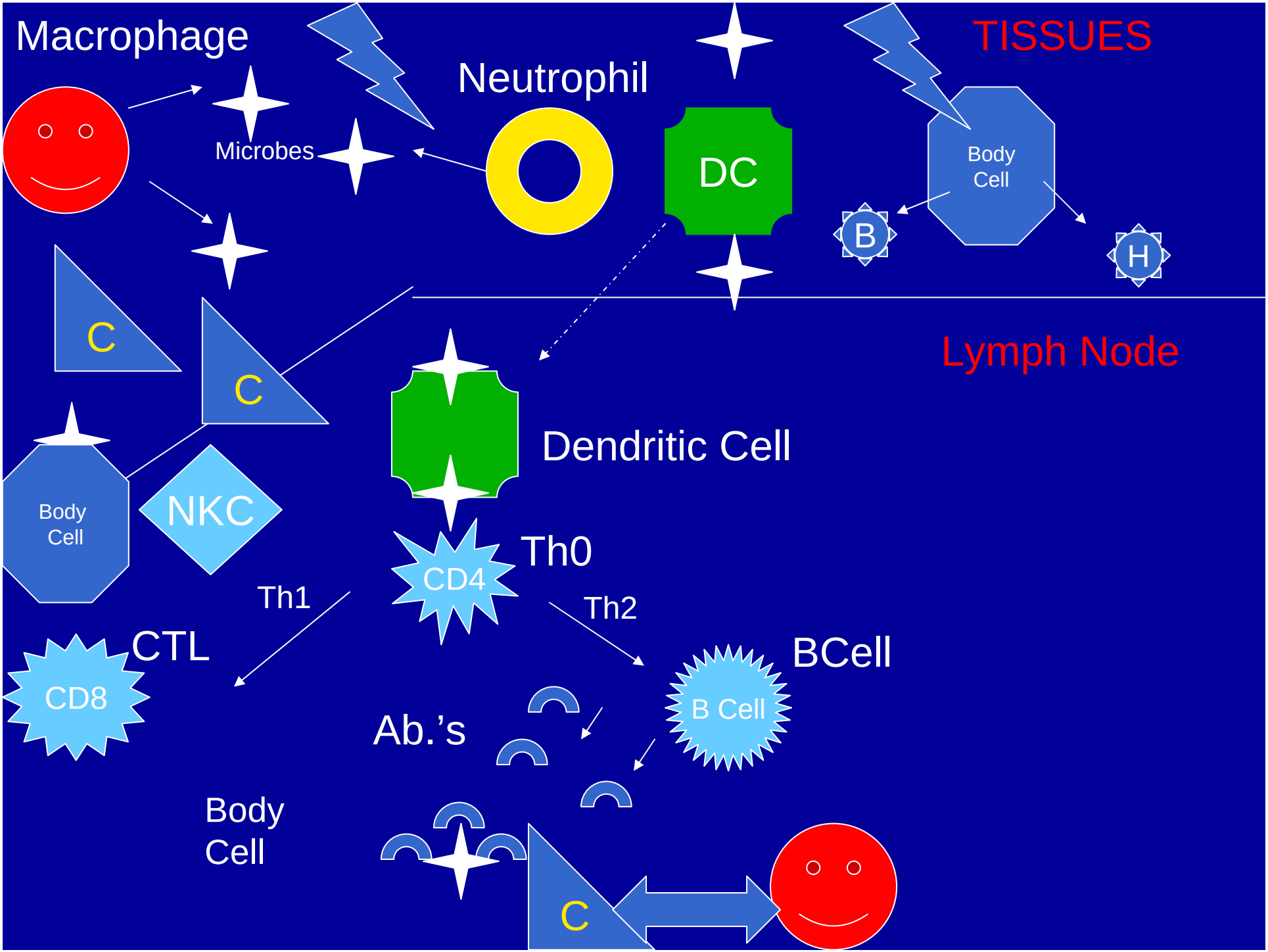
- Immune system, who cares?
- Surgery + anesthesia = immune depression
- Dangerous for patients with pre-existing immunosuppression
- Bad news for ANY patient at risk for postop infections

Review of Immune Basics

- Innate: cells damaged, inflamm mediators, mono/macrophages, neutrophils , NKC's hunt for non-self microbes, dead cells
- Innate cells take antigen back to lymph nodes: turn on "adaptive" lymphocytes
- Adaptive immune response targets specific antigens[even inside body cells] with killer cells, antibodies
- T-lymphocytes, B-lymphocytes

Review of Immune Basics

- Initial **stimulation** Innate Immune cells 2° inflammatory response; PGE2 is produced
- Eventual global **depression** of both responses by anesthetic agents + PGE2
- Innate immune stimulation => Adaptive immune depression (Due to effects of innate effector molecules, e.g. NO; H_2O_2)


Macrophage
Microbes
Neutrophil
DC
TISSUES
Body Cell
B
H
C
C
Lymph Node
Dendritic Cell
Body Cell
NKC
CD4
Th0
Th1
Th2
CTL
CD8
BCell
B Cell
Ab.'s
Body Cell
C

Point A:

Surgery, anesthesia

What's the missing LINK???

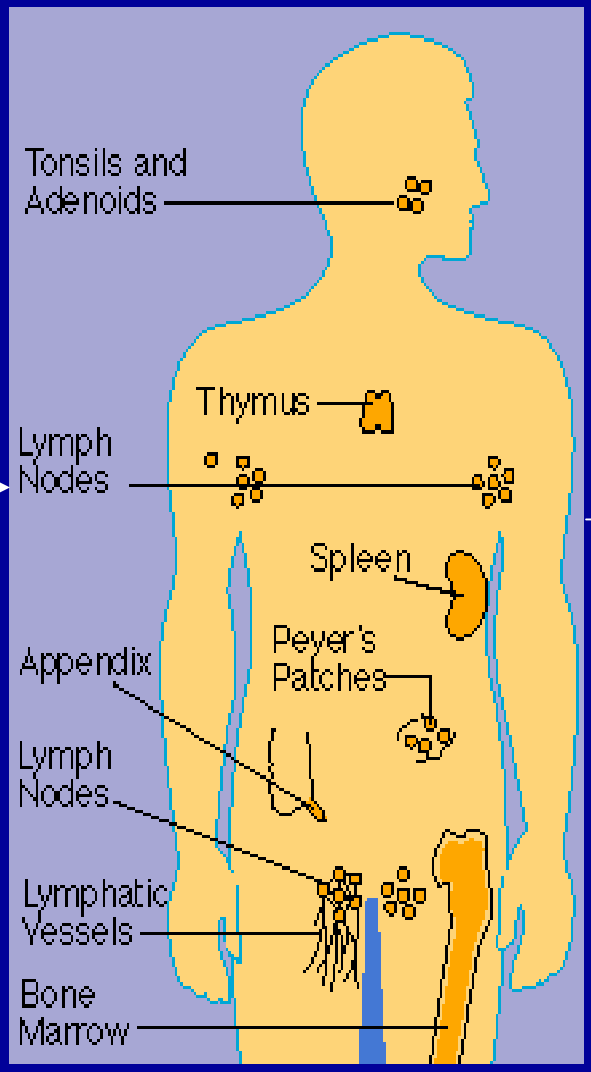
Point B:

Immune Depression

Perioperative

Stressors:

Environmental factors activating the immune system

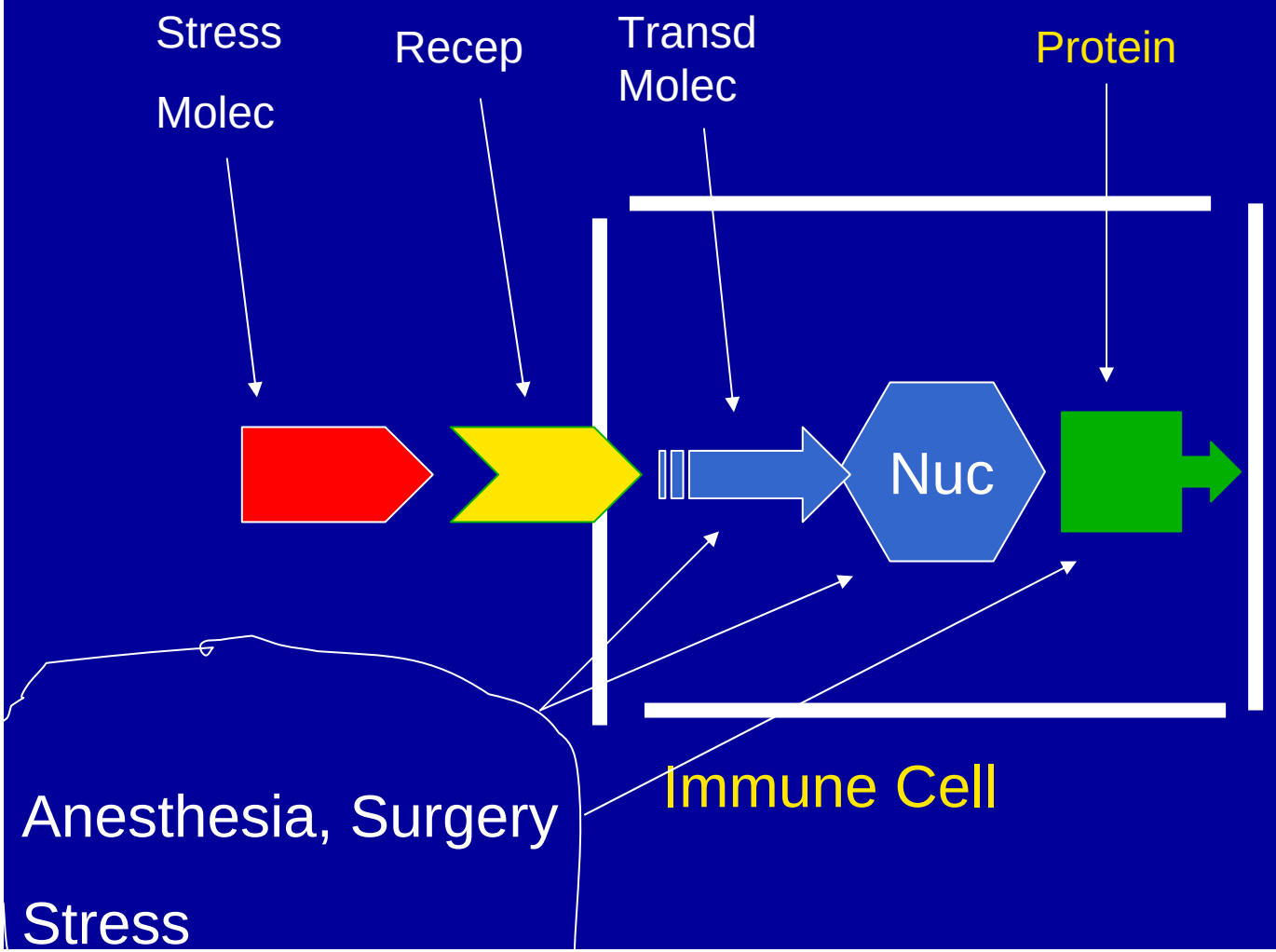


Immune System

Outcomes

Postoperatively

Link between ⇓immune cell function and perioperative stress



Genes --->

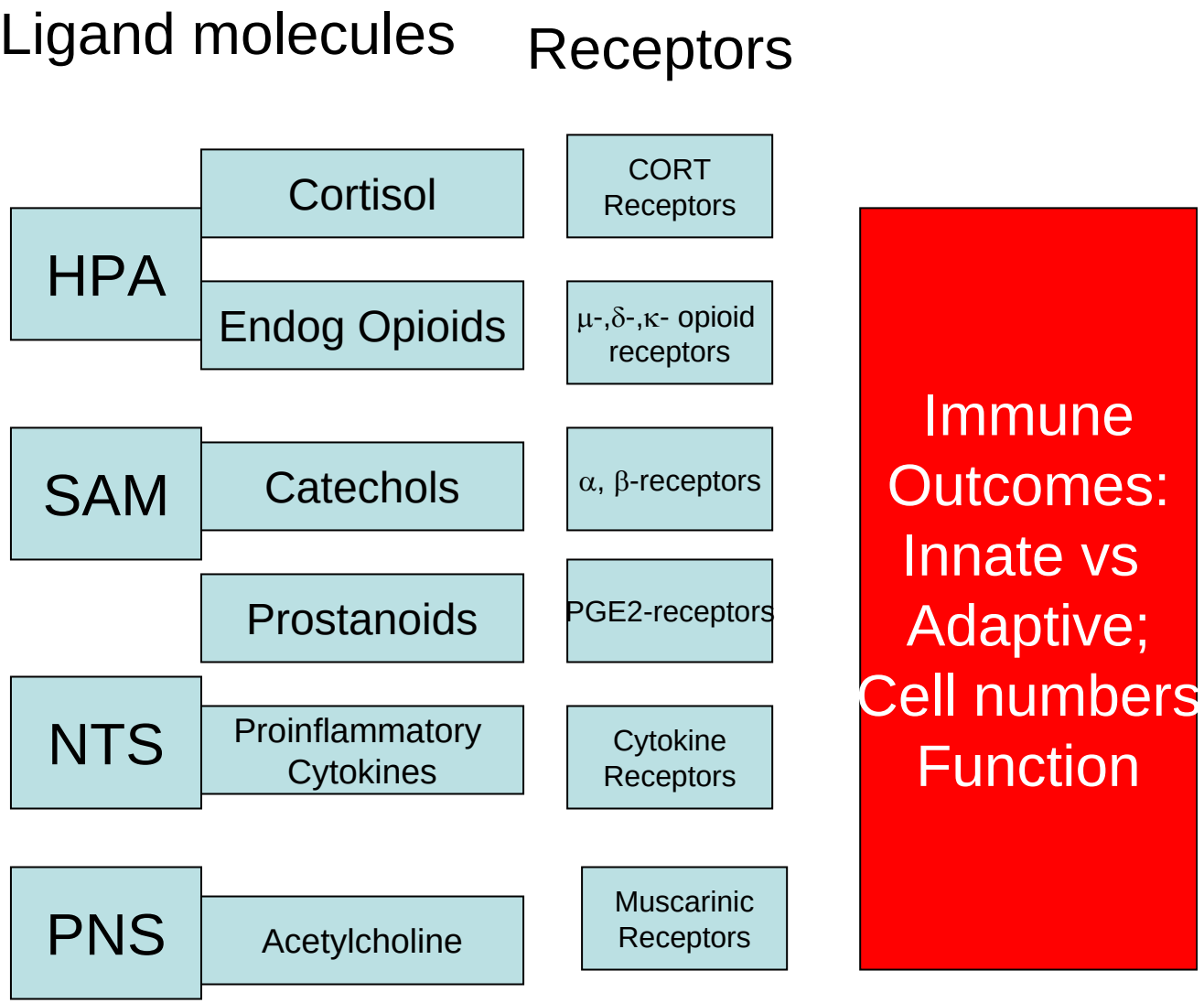
Proteins--->

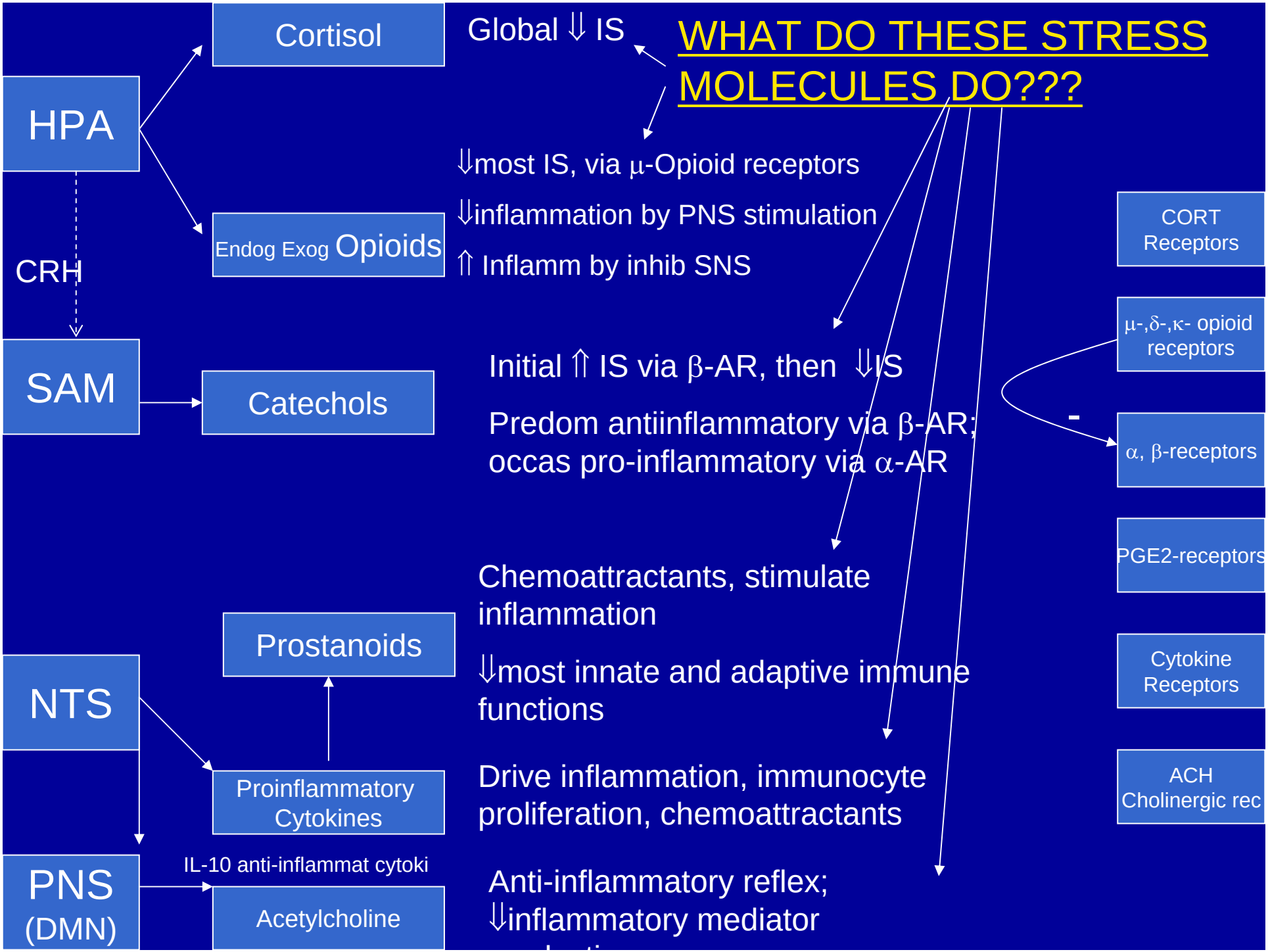
Cell function is affected: inflammatory mediator molecules, phagocytosis, etc.

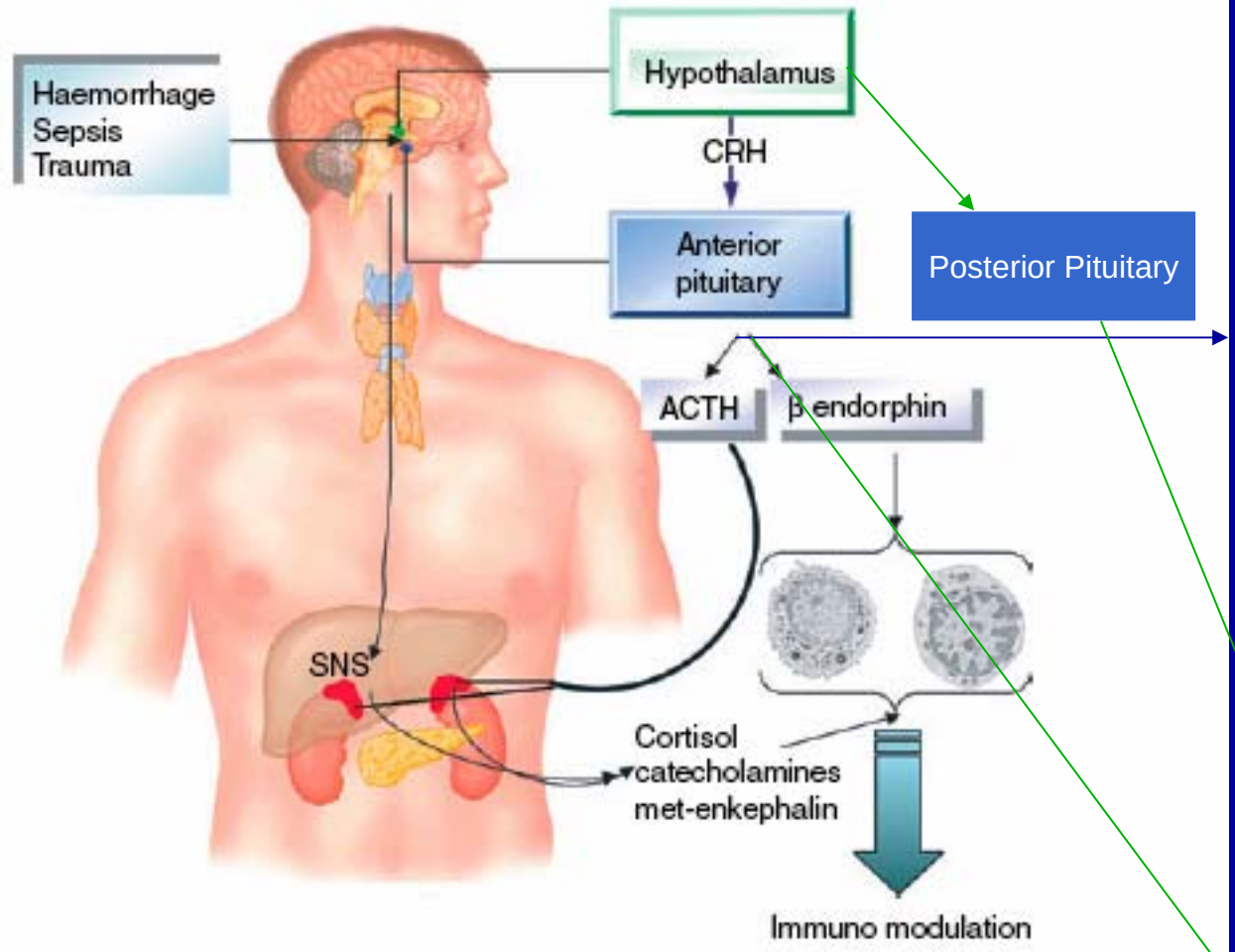
Perioperative Stressors

- Psychological
- Surgical:Pain-stress hormones, hyperglycem
- Surgical:Altered organ perfusion; hypothermia
- Surgical: Inflam-matory Response
- Anesthetic Agents
- Opioids: Endog vs Exogen

Mediating Pathways




Cortisol
Global ⇓ IS
WHAT DO THESE STRESS MOLECULES DO???
HPA
⇓most IS, via μ-Opioid receptors
⇓inflammation by PNS stimulation
Endog Exog Opioids
⇑ Inflamm by inhib SNS
CRH
CORT Receptors
μ-,δ-,κ- opioid receptors
SAM
Initial ⇑ IS via β-AR, then ⇓IS
Catechols
Predom antiinflammatory via β-AR; occas pro-inflammatory via α-AR
-
α, β-receptors
PGE2-receptors
Chemoattractants, stimulate inflammation
Prostanoids
NTS
⇓most innate and adaptive immune functions
Cytokine Receptors
Proinflammatory Cytokines
Drive inflammation, immunocyte proliferation, chemoattractants
ACH Cholinergic rec
IL-10 anti-inflammat cytoki
PNS (DMN)
Anti-inflammatory reflex; ⇓inflammatory mediator
Acetylcholine



Pro-opiomelanocortin

↓

α-MSH

antiinflam

Arginine Vasopressin-

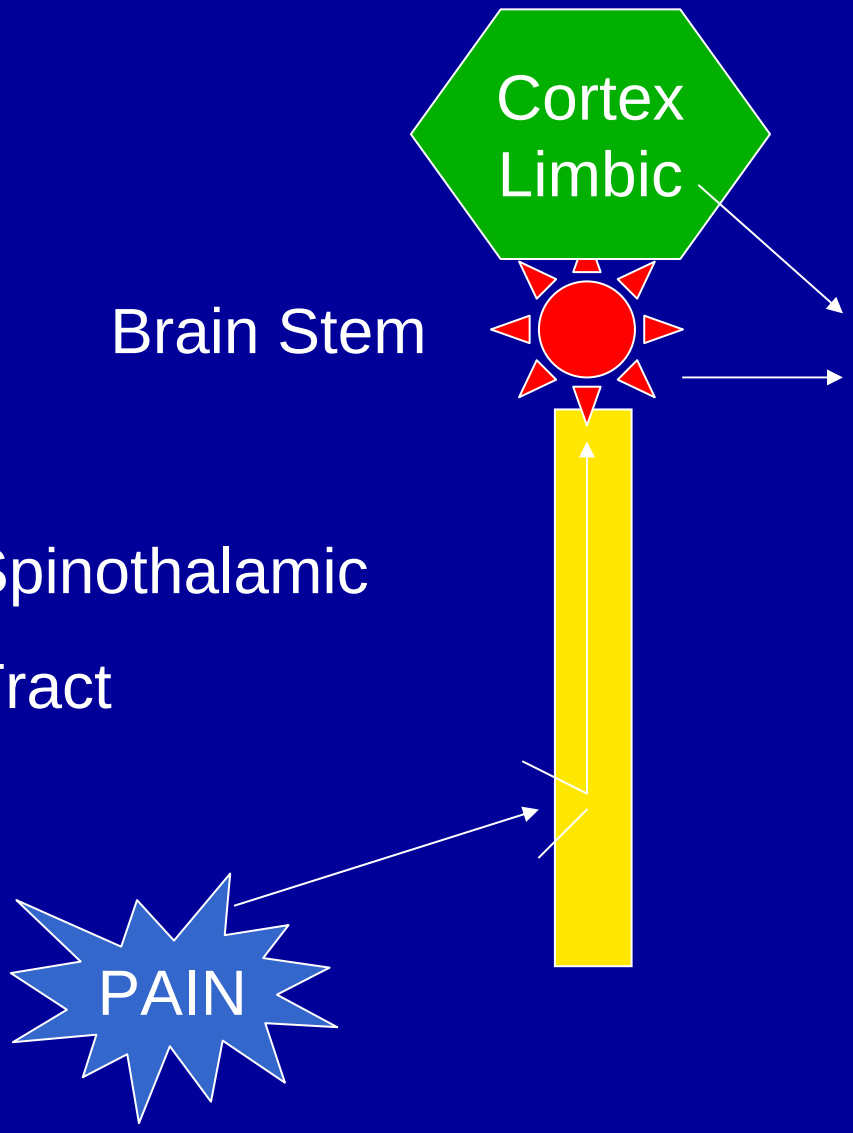
⇑hi conc⇓lo conc

Human Growth Hormone-

Unclear immune effects; ⇑⇓⇔ effects in studies

From Molina, 2005

Pain-related Sympathetic Nervous System Activation



Hypothalamus

+SNS

EPI

NE

β-AR stim= ⇑⇓NKCC, causes ⇑Th2; Anti-inflammatory

α-AR stim= ⇑Th1 = proinflamm cellular immun, better protection infection

Psychological Sources of Perioperative Immune Stress

- FEAR, ANXIETY: pain, loss of control, loss of function, loss of life, altered body image
- Neural pathways from higher cortex/limbic processing centers via median forebrain bundle to paraventricular nucleus of hypothalamus and brainstem to activate stress axes

Surgical Pain: Nociception and its Immune Effects

- Reflex SAM activation=EPI, NE
- Cerebral cortex contribution in PACU
- Reflex HPA activation=CORTISOL
- Hyperglycemia--EPI Glycolysis, CORT:
  - ⇓Immune cell func.,activates mediators
- Brainstem activation: proinflamm mediators?
- Pain and Stress response proportional to size of surgical intervention
- Remember: Opioids combat these effects!!

Pain and Inflammation: A relationship?

- Inflammation--->pain; but does

Pain--->inflammation?

- Griffis, Kaufman et al.: Preliminary evidence of relationship.
- Pilot study: 10 healthy subjects, 45 min of acute earlobe pain, sig elevation epi and CD8+CD11a+ cells, correlated with pain perceptions. Conclusion: nociceptive pain may cause increased cellular adhesion molecule expression, which can drive inflammation.

Invasive Surgery: End-organ and Hemodynamic Effects

- Invasive surgery: significant organ manipulation ⇑**Inflammatory Response**.
- Massive fluid shifts; blood transfusion. ⇓ organ perfusion; ischemia.
- Blood pressure ⇑⇓: SNS activation
- Hypothermia: known immune depressant; vasoconstric ⇓ O2 tension to immunocytes; cell functions depressed in cold environment
- Laparascopic approaches avoid many of these potential complications, immune-sparing

Inflammatory response to surgical intervention

- Arachidonic acid>>COX1,2>>**PGE2** (direct lymphocyte depressant)
- Arachidonic acid>>Lipo.ox>>Leukotrienes
- Damaged tissues release other mediators (histamine, bradykinin)
- Innate cells STIMULATED==⇑Inflammation as innate cells contribute mediator molecules
- Eventual DEPRESSION of innate and lymphocyte adaptive cells
- **Bigger** the **surgery**, **bigger** the **inflammation**

Anesthetic Agents and Immune Function

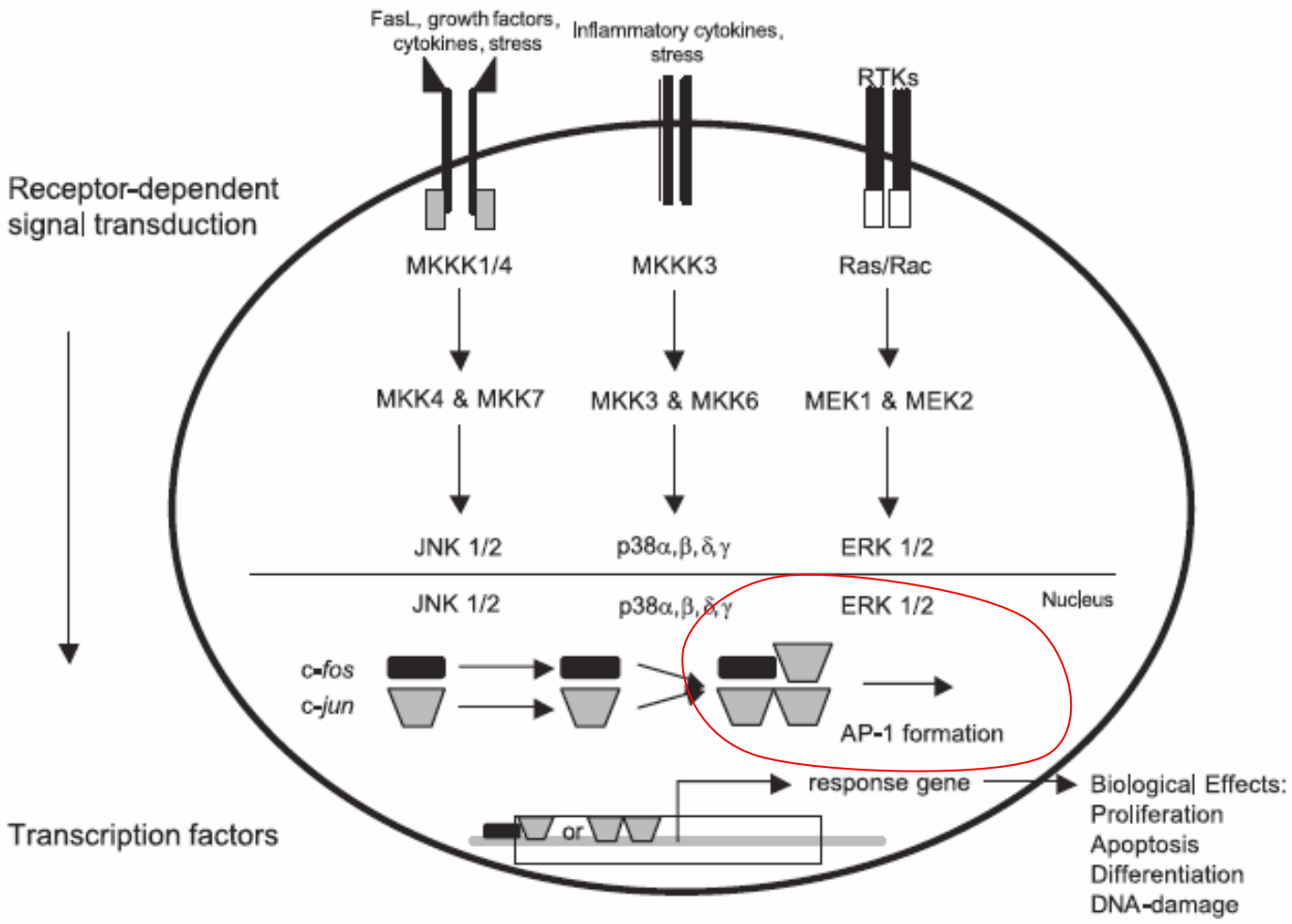
- Historically, perioperative immune suppression has been observed (Loop, 2004; Schneemilch,2005)
- Effects of inhaled agents=⇓immune cell functions
- N20 and Potent: Halo Iso Desflurane all ⇓ IF

  Sevoflurane: ⇓AP-1 transcription factor

  Attenuated intracellular Ca++ release=⇓iNO synthase; ⇓interferon NKC response=generally antiinflammatory, but not immune-sparing--directly suppressive of adaptive immunity as well.

Sevoflurane specifically interferes with transcription factor

functions; inhibit Activator Protein-1 (AP-1) pathway Loop et al., 2004. Sevo also causes activation of caspases and mitochondria membrane breakdown====apoptosis.



Anesthetic Agents

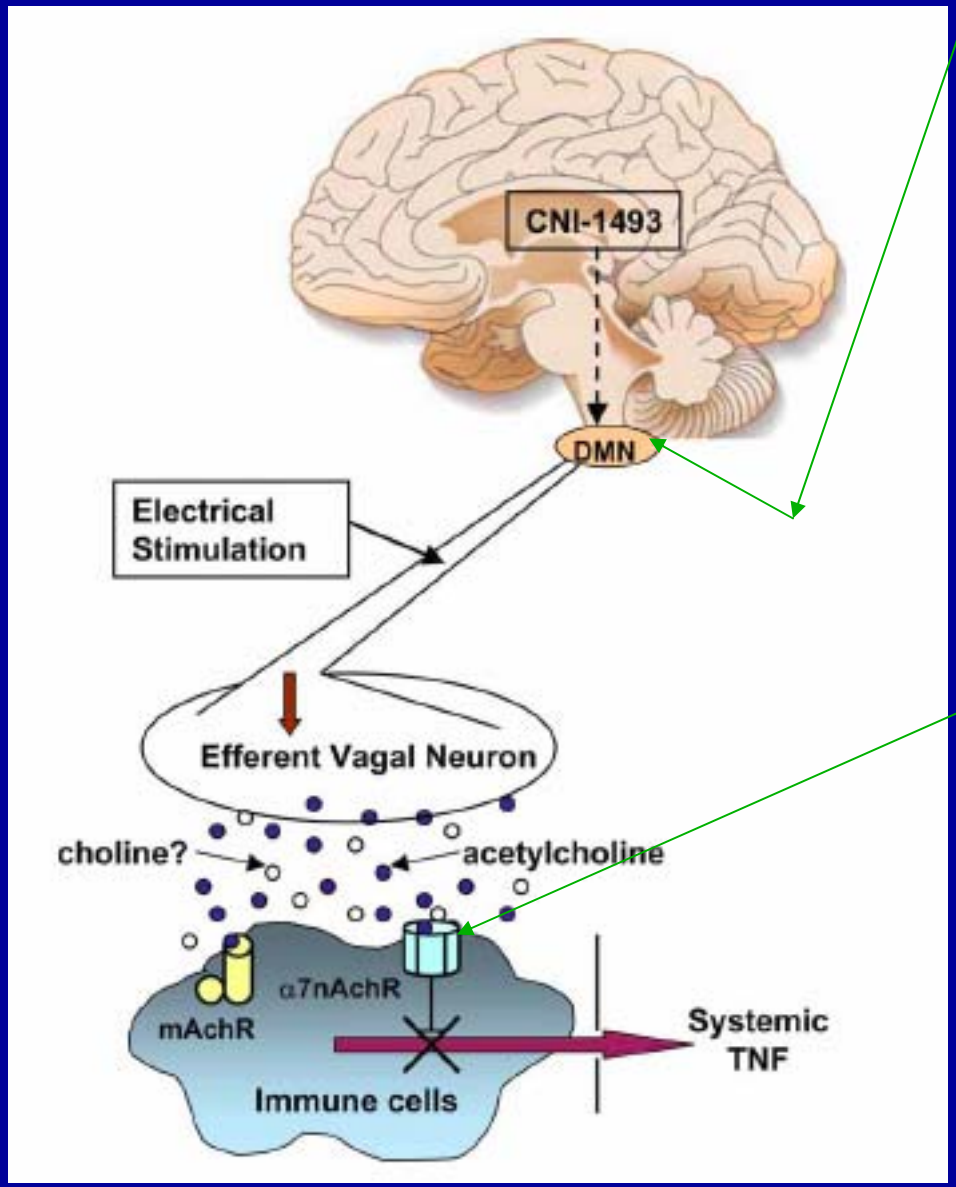
- Local anesthetics--inhibit inflam cascade multiple levels--via non-Na+chan receptors; M1 muscarinic and G-prot coupled receptors at low concentrations (Homburger)
- Intravenous
  - Thiopental:⇓cell prolif, IL-2 prod (Schneemilch)
  - Propofol: ⇓cell prolif, IL-2 prod (Schneemilch)
  - Ketamine ⇓mΦ function 2°mitochondrial membrane potential reduction(Chang)
  - Etomidate ⇓Tcell proliferation to PHA(Devlin)

Anesthetic Agents

- **In absence of surgery**, Procopio et al (2001) found NO significant effect of GA by mask (thiopental, isoflurane) or lumbar epidural anesthesia with 1.5% lidocaine as compared to control grp on multiple immune parameters *in vivo (exam immune cells of volunteers)*
- *In vitro* exposure of immune cells to these and other anesthetics caused significant impairments in similar immune measures.

Opioids: endogenous and exogenous--complex immune effects

1. Opioid activation can ⇑inflammatory response of innate cells (μOR's down-regulate β-AR's)
2. Opioids can ⇓inflammatory response of innate cells (cholinergic receptor up-regulation)
3. Opioids--> ⇓ T cell func.; ⇓Protein Kinase C (Molina; Homburger)
3. Recent studies: Fentanyl in lab ⇑NKCs; following heart surgery ⇓ NKCs
4. Confusing evidence due to differences in study conditions; varying specific drug effects; and opposing autonomic mechanisms of effect.



Pavlov & Tracey, 2005

Opioids may exert an

anti-inflammatory, immunosuppressive effect by stimulating the medullary vagal dorsal motor nucleus. ACH molecules generated by efferent vagal output, interact with a subtype of cholinergic receptor to inhibit proinflammatory cytokine (PIC) release.

Opioid drugs, pain, and immune function: Bottom Line

- Though opioid drugs alone suppress NKC function via a specific naloxone-reversible mu-opioid receptor-mediated effect, **interaction** of this effect in the presence of pain-related catecholamine/stress molecules is UNCLEAR:
- Opioids **in presence of pain** may ⇓stress, ⇓neuroendocrine response and ⇑immune func; animal studies document ⇓metastasis when morphine admin to animals postop--better NKC function due to less stress?? Unclear causal pathway.
- **TREAT PAIN EFFECTIVELY--IT CAN ONLY HELP!!**

Opioids with favorable immune effects

- Buprenorphine (Sacerdote, 2006). Partial μ-agonist/antagonist.
- Tramadol (Sacerdote, 2000; Beilin,1998). μ-agonist and re-uptake inhibitor of norepinephrine and serotonin
- Favorable immune effects (lack or, or mild ⇓immune cell function) mechanism unknown, but lack of pure MOR activity is a clue

Regional Anesthesia and Immune Function

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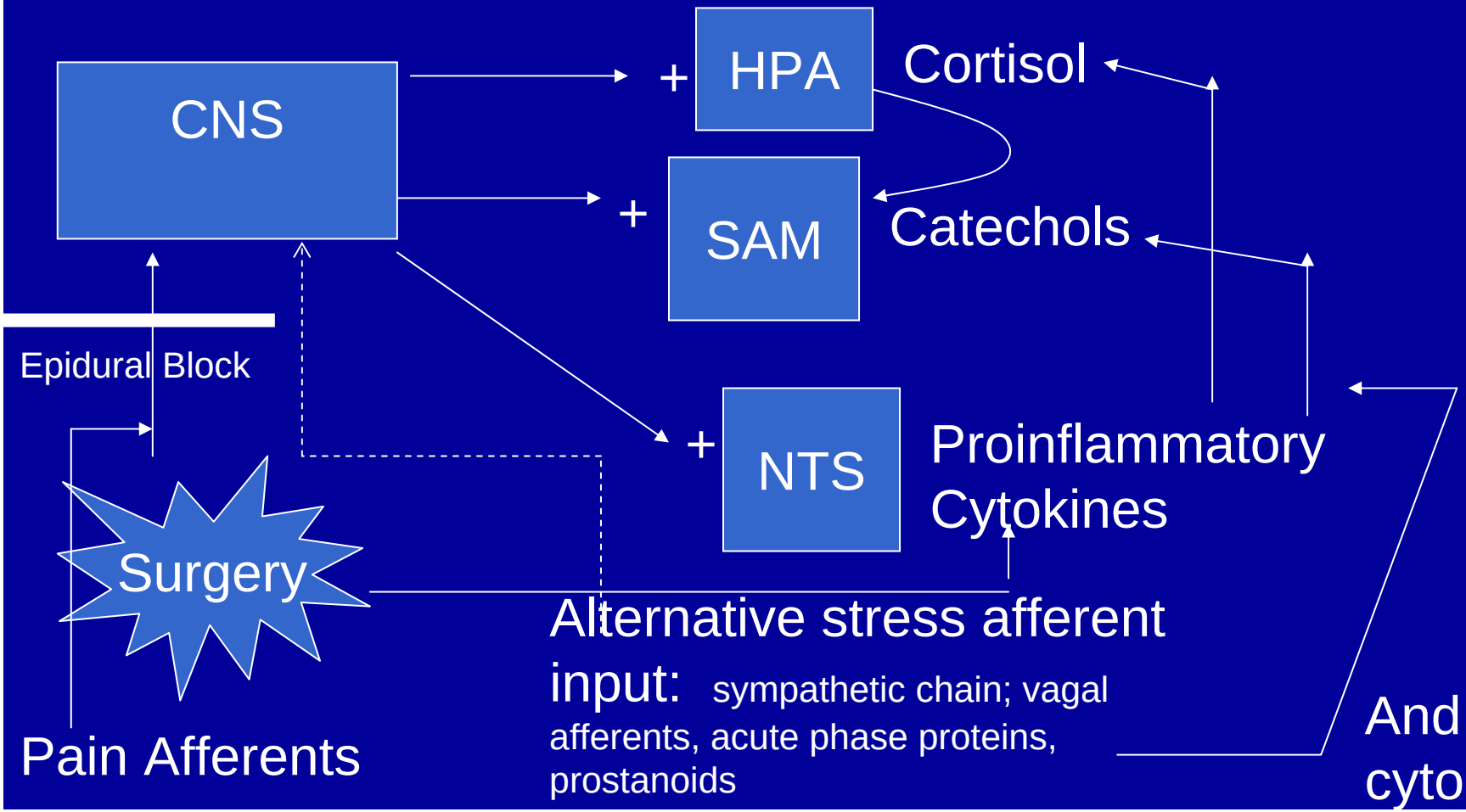
GA + epid; GA + epid +/- PCEA; PCEA after GA

Local anesthetics +/- opioids

Regional Anesthesia and Perioperative Immune Function

- Review of these studies reveals:
  - Epidural anesthesia +/- opioid can prevent some perioperative immunosuppression, possibly modulate inflammatory changes
  - Seems to work best with lower body surgery; upper abdom/thoracic surg no difference in postop immune status GA vs epidural
  - In major surgery upper body, too many unblocked sensory afferents, sympathetic branches, vagal afferents, and too many mediator molecules produced = humoral stimulus to CNS stress axes

Limited Beneficial Immune Effects of Epidural Analgesia for Thoracoabdominal Surgery



Conclusions and Clinical Implications

- Stressors result in endogenous (and we administer) exogenous compounds that produce perioperative immune depression via receptor-mediated pathways.
- No evidence of significant morbidity in healthy populations, few studies = mild ⇑ infections correlated with periop immune depression
- Immunosuppressed populations may be at increased risk for sequelae; no data

Clinical Implications

- In selected patient populations, the preservation of immune function is a more serious priority
- Pre-existing immune system abnormalities predict greater risk of postoperative morbidity

Populations at risk

- HIV-infection with AIDS
- Organ transplantation with iatrogenic global immune suppression
- Pre-existing immune suppression from chronic disease or malnutrition
- Cancer--blood cancers, even solid tumor CA; intact immune responses may ⇓ metastasis risk; NKC immunosurveillance
- Severe trauma; extremely invasive surgery

Recommendations for anesthesia care

- Provide preoperative emotional support for patients, along with an effective premed, ⇓cortical and limbic input to stress response
- Maintain normothermia, especially in major surgery
- High FiO_2, maintain tissue oxygenation
- Treat hyperglycemia aggressively in hi risk pt
- Consider epidural analgesia and PCEA in suitable patients at risk for immune sequelae

Recommendations

- Treat pain effectively, reducing stress response can only be beneficial to IS, regardless of direct opioid effects.
- NSAID analgesia when possible: block PGE2 immunosuppression; restrain inflammatory process and nociceptor upregulation (Mahdy,2002).
- Future opioid compounds may have a more favorable immune effect profile
- Consider use of novel opioids (tramadol and buprenorphine) in selected populations

Severe SIRS, SICU Care

- Consider immunomodulation
- Pentoxifylline (Trental®): PDE inhibitors, stops proinflamm cytokine production (TNFα)
- DHEA-estrogen precursor restores cellular immunity via estrogen receptors (Angele,2005)
- Flutamide--androgen blocker prevents decreased cellular immunity associated with male sex steroids
- G-CSF-leukocyte growth factor restores monocyte supply

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