

Psychoneuroimmunology

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What is PNI ?

- Multidisciplinary study of how the emotions, nervous system and the immune system interact
- PNI also includes endocrinology, infectious disease rheumatology and gastroenterology
- Sometimes referred to as psychoneuroendocrinology or psychoendoneuroimmunology
- Subfield of molecular biology, but has been coopted by the alternative, mind-body medicine movement

History of PNI

- Early physiologists noted the effects of emotion on GI function in animals, specifically cessation of motility
- Hans Selye did extensive research on stress and the HPA axis between 1936 and 1974 (>1k papers, 7 books)
- Selye described the “General Adaptation Syndrome” with enlarged adrenals, gastric ulcers and atrophy of lymph org
- In mid 1900’s studies showed poor immune function in psychotic pts (poor response to vaccine and low WBC)

History of PNI

- G. Solomon coined term “psychoimmunology” and wrote “Emotion, Immunity and Disease” in 1964
- In 1975, Ader and Cohen showed that mice could be classically conditioned into full immunosuppression
- In 1981, David Felten found ANS nerves in the thymus and spleen connecting to macro, lymph and mast cells
- In 1985, Candice Pert demonstrated neuropeptide and neurotransmitter receptors on immune cells

Basics of PNI

- Nervous system influences the immune system via the HPA axis and the Autonomic Nervous System
- Immune system influences the emotions and nervous system via pro-inflammatory cytokines (PICs)
- PICs (IL-1, IL-2, IL-6, IL-12, ENF-g, TNF-a) cross the BBB and induce “Sick Behavior” via the hypothalamus
- Sick Bx includes fever, lethargy, depressed mood, anxiety, anorexia, hypersomnia, hyperalgesia, decrease motivation, grooming and concentration

Effects of Stress

- Brief acute stress < 30 min (parachuting) seems to improve some immune function (NK cells)
- Chronic stress as brief as a couple of days clearly worsens most immune function (NK cells, T cells)
- Chronic stress worsens immune function; increased infections, HIV prog and cancer incidence and prog
- Chronic stress slows wound healing in humans
- Chronic stress also increases auto-immune d/o's in animal models, but human evidence is less clear

Is All Stress the Same?

- Control or illusion of control over stress protects immune function in both lab animals and humans
- Strong social support and high social status seem to be protective of immune function
- Low SES, obese or racial minority have elevated cortisol and lower immune function
- Being observed during a task, feeling self conscious or acute social status threat lower immune function

Inflammation and the Brain

- Inflammation has been implicated in many brain disorders (MDD, BPAD, autism, Parkinson's, AD, chronic pain)
- Injection of PICs causes dysphoria, anhedonia, fatigue, apathy and feelings of helplessness
- 5 studies have shown augmentation with a cox-2 inhibitor improves response in severe depression
- SSRI, SNRI, TCA and meditation have been shown to decrease pro-inflammatory cytokines

Autoimmune CNS D/o's

- Multiple sclerosis and transverse myelitis have twice the rate of MDD as sick controls (25% 1yr/50% lifetime)
- Autopsy studies show active vasculitis even during “remission” periods of MS and TM
- Depressed MS pt's lymphs have 2x the antimyelin activity in vitro, normalizes after treatment of MDD
- Li and Prozac (combo best) prevent progression of MS in animals, Prozac prevents new lesions (human)

Multiple Sclerosis

- Severe loss (of a child) increases MS rate 50% in 1st yr, prolonged bereavement (7-15yrs) increases RR to 2.13
- Most studies of childhood PA don't show increased risk, but new studies looking at emotional neglect do
- War exposure (refugees) triples the MS relapse rate
- Fatigue causes more disability than lost mobility
- Group therapy, 1 to 1 bx interventions and exercise show decreased fatigue, relapse rate and lesion form

Autoimmune Disorders

- Chronic stress seems to play a role in autoimmune disorders, via local dysfunction/disinhibition of IS
- Mechanisms still being worked out, better studied in animal models, may not be the same in different d/o's
- Rats models of IBD show increased inflammatory response to TNBS exposure following 4 days of stress
- Stress or low dose rechallenge induces colitis in the previously stress rats, but not controls (CD4 lymphs)

Inflammatory Bowel Disease

- Early maternal deprivation increases severity of colitis in rats both in initial and rechallenge colitis
- Stress rechallenge colitis in rats can be blocked with desmethylinipramine (Desipramine)
- Human studies have shown increased inflammatory markers in gut and serum vs controls in cold exp test
- Antidepressants, PPAR γ agonists and probiotics also show improved integrity of intestinal barrier

Evidence in Cancer

- Strong evidence in animal models, but mixed in humans (trouble replicating positive results)
- More recent studies have broken out breast CA pt's based on oxytocin levels (high with social support)
- Only low oxytocin level pt's show a response to txt (support groups, therapy and massage)
- Survival rate studies of interventions for low oxytocin pt's currently ongoing

Neuroparasitosis

- *Toxoplasma gondii* infects mice and rats via cat feces then hijacks the rodents CNS to inhibit fear of cats
- The rodents also have increased testosterone levels and are attracted to the smell of cat urine
- The rodent is eaten by a cat then infects the cat where it sexually reproduces
- The parasite often passes to undesired hosts (dead end host) such as humans and livestock

Toxoplasma in Humans

- The parasite migrates to the brain where it reproduces asexually and forms cysts (for life)
- In humans, the personality effects tend to increase over time, however RH+ blood may be protective
- Reaction times are slowed and show increase MVA's in multiple retrospective and one prospective study
- Infected mothers have more sons and children with Down's syndrome

Toxoplasma in Humans

- Infected males are 3cm taller on average and are rated as having more masculine/dominant faces
- Over 40 studies have shown increase rates of infection in schizophrenic patients than controls
- Infected schizophrenics have more positive sx than non-infected schizo and different brain anatomy
- Tg has an enzyme that increases a DA precursor, minocycline is currently being studied (case reports)