MICROBES, BRAIN AND BEHAVIOR

Krister Kristensson

Department of Neuroscience,
Karolinska Institutet,
Stockholm, Sweden

”Behavioural Neurovirology””
HOST-PARASITE INTERACTION

i/ The “sickness response” favour survival of the host

ii/ Manipulation of host behavior by the microbes help them complete their life cycle.

iii/ Pathology, good for nobody
What behavior changes could favor the host during an infection?

Reactions that could serve to combat the microbes in the infected individual?
Why are we sick when we are attacked by microbes?
SOME MICROBES CAN INVADE THE BRAIN
BUT MOST MICROBES DO NOT AND STILL WE FEEL SICK
SICKNESS RESPONSE

• Increased sleep
• Decreased food/water intake
• Pain-related behavior

**Advantage to the host**

• Conserve energy to be used for **fever**, which may inhibit microbe multiplication
Central Nervous System

Immune System

Neuroendocrine System

Peptides Hormones
Peptides Neurotransmitters
Cytokines

Activation via Receptor Molecules
CYTOKINES

Highly inducible, secreted proteins mediating intercellular communication in the immune system
Infected cell with MHC I displaying normal host and viral peptides.

Infected cell with Tc cell bound to MHC I and viral peptides via T-cell receptor and CD8 receptor protein.

Host cell

Viral pathogens

IgG Fc receptor

T-cell receptor

CD8

Interleukin receptor

B cell
CYTOKINES

Pro –inflammatory cytokines
Tumor necrosis factor (TNF) – \( \alpha \)
Interleukin (IL) -1, -4, -12
  Il -12  Th1 cytotoxic response
  Il -4    Th2 humoral response
Interferon (IFN) - \( \gamma \)

Anti –inflammatory cytokines
Interleukin (IL) – 10, - 1receptor antagonist
Areas involved in sleep regulation

- Forebrain areas key to the neuropsychology of dreaming
  - Prefrontal cortex: Ventromedial, Dorsolateral
  - Anterior limbic structures: Amygdala, anterior cingulate, ventral striatum
  - Posterior cortices: Inferior parietal, Visual association

- Thalamocortical control of NREM sleep rhythms; EEG activation and deactivation

- Hippocampal–cortical control of memory consolidation

- Origin and expression of circadian rhythms
  - Hypothalamic nuclei: Suprachiasmatic, Subparaventricular, Dorsomedial

- Diencephalic control of sleep onset
  - Hypothalamic nuclei: Ventrolateral preoptic, Lateral, Tuberal mammillary, Basal forebrain

- Pontine control of the REM–NREM cycle
  - Mesopontine nuclei: Laterodorsal tegmental, Pedunculopontine, Dorsal raphe, Locus coeruleus
How can cytokines reach diencephalic and brainstem nuclei?
Blood-brain barrier
Increasing permeability of BBB

Through activated white blood cells

Activating endothelial cells to secrete prostaglandins into the brain
Cells within the brain may also secrete inflammatory cytokines, e.g. activated microglia, perivascular macrophages and maybe astrocytes and some neurons...
Circumventricular organs – lack BBB

ME - median eminence
PP - pituitary gland
Confusion, malaise, headache

PGs

Sickness behavior
ACTH response

NTS

VLM

Liver

Anorexia

PGs

Nodose ganglia

Vagus nerve

PGs

Hepatic and lung macrophages

Model: intraperitoneal LPS and cytokines
local infections (e.g. peritonitis, pneumonia)
Cytokines may reach the brain

Through the **BBB** by

  *i/* increasing its permeability
  *ii/* activated white blood cells
  *iii/* activating endothelial cells to secrete prostaglandins

Through **retrograde axonal signalling** from circumventricular organs or via vagus nerve
Host combats microbes

Fever

Inflammation

Immune response

Innate

Adaptive
b/ behavior changes that can limit the microbe spread to other individuals?
• Social withdrawal
• Decreased sexual activity
c/ **Behavioral Alterations and Avoiding Parasites**

- Moving away
- Joining a group
- Swatting, biting, slapping
- Using camouflage – zebra stripes
- Washing hands
- Mate selection – parasites are likely to have favoured evolution of sex itself
ii/ What behavior changes induced by the microbe in a host could favor microbe survival and spread?
Parasite manipulation of the host

• Altered locomotor activity
• Conspicuous behavior/appearance
• Changes in social behavior
• Changes in foraging behavior
• Changes in odor attraction

Advantage to the parasite

• Facilitate spread of parasite from intermediate to definite host by increasing chances for predation
• Conserve energy to be used for parasite multiplication
Examples of Behavior that Favour Parasite Spread

1. Trematode-infected isopodes show no evasive response to simulated predator. 
   *Hansen & Poulin Parasitol Res 97:242-246, 2005*

2. Trematode-infected ants climb to top of grass at night

3. Rabies virus causes aggressive biting behaviors in dogs
“Even by rudimentary surveillance, one person dies from rabies each 15 minutes, and more than 300 others are exposed”

Rupprecht et al., Lancet Infect. Dis., 2002
a rabid dog:
hypersalivation and violent aggression
Negri bodies described in 1903 by Adelchi Negri (1875-1912)
MICROBES OF MAJOR CONCERN IN AFRICAN COUNTRIES

HIV- neuroAIDS

*Plasmodium falciparum* – cerebral malaria

*Trypanosoma brucei* – sleeping sickness
Behavior alterations favour:

i. Host

ii. Parasite

iii. None
HIV

Kaul, Garden, Lipton, 2001
Clinical signs of HIVD:

1. impaired memory and concentration
2. psychomotor slowing.
3. apathy and social withdrawal
4. motor deficits – ataxia, tremor, weakness.

Terminal stages: severe dementia, autism, incontinence and paraplegia
Cerebral malaria

- Causes death of 1.5-2.7 million persons every year
- *Plasmodium falciparum, vivax, ovale and malariae* are infectious to Man
- Parasitemia;
- **Coma** for 30 minutes or more
- Adhesion of erythrocytes to endothelial cells, secretion of "tumor necrosis factor"-α, phospholipids and malaria toxins
*P. Falciparum* in erythrocytes

(from Camillo Golgi, Pavia)
Tissue effects
- increase of blood brain barrier permeability
- signaling?
- nitric oxide release?

Endothelial activation
- by parasite induced release of cytokines
- by binding of pRBC to endothelium

Erythrocyte adherence (rosetting) to receptors HS, blood-group A, blood-group B, CR1/CD35, CD36
- with IgM, IgG, fibrinogen

Circulating cellular bi-products siCAM-1, big endothelin etc.

Endothelial adherence (cytoadherence) to receptors CD36, TSP, CSA, ICAM-1, PECAM-1/CD31, VCAM-1, E-selectin
- by rolling on ICAM-1, CD36, VCAM-1
- by immobilization on CD36, CSA
- by adhesion strengthening CD36-ICAM-1 synergy

Vascular occlusion?
Other symptoms of cerebral malaria

- Psychomotor agitation
- Desorientation, hallucinations
- Delayed cerebellar ataxia
- Complications: fatigue, auditory problems, epilepsy, cortical blindness
- Learning disabilities and behavior disturbances
Cerebral infections

1. HIV
2. Cerebral malaria
3. African trypanosomiasis
African Sleeping Sickness: Disturbances in Sleep and the Circadian System in Clinics and Experimental Models
Sleeping sickness
Human African trypanosomiasis

- More than 300,000 deaths per year in sub-Saharan Africa
- *Trypanosoma rhodesiense* and *gambiense*
- *Les Glossines* or tse-tse fly
- Distruption of sleep/wake cycle
- Inflammation in the white matter of the brain
Disrupted EEG sleep pattern in HAT

A. Buguet et al.
Hypnogram obtained from rat EEG recordings

Control

T. b. brucei

(Grassi-Zucconi et al. 1995, Br Res Bull 37:123-29)
Sleep and EEG:

- Hypersomnia does not occur
- Fragmentation of the sleep-wake pattern
- Reduction of Slow Wave Sleep
Disturbances in circadian rhythms

- Fragmentation of sleep/wake pattern
- Disturbed secretion of prolactin and cortisol
- Functions of the **suprachiasmatic nuclei**, which are the pacemaker of circadian rhythms, are altered in rats infected with *T. b. brucei*
The suprachiasmatic nuclei (SCN) in the rat
Cerebral infections

1. Cerebral malaria
2. HIV
3. African trypanosomiasis
4. Toxoplasmic encephalitis
Fatal attraction in rats...
Rats, cats, people and parasites.


Children with latent toxoplasmosis had on average a lower IQ (93) than controls (110). *Alford et al 1974*

Infected men: higher tendency to disregard rules of the society, more suspecting, jealous and dogmatic.

Infected women: more warm-hearted, out- and easy-going, but also more conscientious, persistent, moralistic and staid. *Flegr et al 1994, 2000*
PARASITIZED HOST BEHAVIOR

Pro-host: - “sickness response” (sleep, loss of appetite, pain - fever);
- social withdrawal

Role of cytokines and how they may circumvent the BBB

Parasite avoidance behavior

Pro-parasite behavior: Trematodes, rabies

HIV, cerebral malaria, sleeping sickness and toxoplasma infections
Microbes can cause behavior alteration of the host.

Can human behavior disorders be caused by microbes?
Time to stop
Mad cow
Bird flu
"NO, I'm not mad....... just very, very angry"
ICEBERG CONCEPT OF INFECTION

Below Visual Change

- Exposure without attachment and/or cell entry
  - Infection without clinical illness (asymptomatic infection)
  - Exposure without infection

Below Change

- Viral multiplication without visible change or incomplete viral maturation
  - Infection without clinical illness (asymptomatic infection)
  - Exposure without infection

Discernable Effect

- Cell dysfunction
  - Inclusion body formation or cell transformation
  - Lysis of cell

Host Response

- Death of organism
  - Classical and severe disease
  - Moderate severity mild illness

Cell Response*
Toxoplasma (red) astrocyte (green)
Paraventricular nucleus

i/ parvocellular neurons - corticotropin - releasing hormone and release – inhibiting neurons (dopamin, somatostatin)

ii/ magnocellular neurons - oxytocin, vasopressin

Periventricular neurons

Gonadotropin -, growth hormone -, and thyrotropin – releasing hormones
How can the neuroendocrine system affect the immune system?
Stress System
Stimulated by cholinergic and serotonergic neurotransmitters
Inhibited by GABA–benzodiazepine and POMC peptides

Paraventricular nucleus
CRH
AVP
Pituitary
Arcuate nucleus
POMC peptides
Corticotropic
Epinephrine
Norepinephrine
Neuropeptides
Sympathetic ganglion
Norepinephrine
Neuropeptides
Dorsal-root ganglion
Locus caeruleus (noradrenergic system)
Norepinephrine
Hypothalamic-pituitary adrenal (HPA) axis
Glucocorticosteroids are anti-inflammatory

• down-regulate release of cytokines from inflammatory cells

• down-regulate cytokine receptors on target cells
Summary of sites for immune–brain interactions
# Control of Inflammation

<table>
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<th>Organism</th>
<th>Glucocorticosteroids</th>
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<td>Tissue</td>
<td>Anti-inflammatory cytokines</td>
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<td>Cell</td>
<td>Supressors of Cytokine Signalling (SOCS)</td>
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Inflammation – IN FLAME
Cytokine–induced sickness behavior

- Increased sleep
- Decreased food intake
- Pain–related behavior
- Fever
- Social withdrawal
- Decreased sexual activity
Increased sleep
Decreased food/water intake
Pain-related behavior
Fever
Social withdrawal
Decreased sexual activity
Sleep induced by IL -1β

Feeding behavior — ventromedial and lateral hypothalamic nuclei; leptin activated neuropeptide Y neurons in arcute nuclei. Cytokine effects??

Pain –related behavior — nociceptive nerve fibre projections and connetions in the CNS. Induced by IL -1β and IFN -γ
c/ how would you design a research project to find out:

• areas in the brain that could be involved in generation of fever

• factors that may operate to induce the changes?
Fos-like immunoreactivity after LPS administration

Elmquist et al. TINS 20, 565-569, 1997
Preoptic sites at which prostaglandin produces fever and cyclooxygenase inhibitor blunts LPS-induced fever
Effects of *Trypanosoma brucei brucei* infections and cytokines on the biological clock
Retzius building

Gustaf Retzius

Cajal – Retzius cells
Toxoplasmatic encephalitis

- 25-50% of *Toxoplasma* seropositives infected with HIV develop toxoplasmic encephalitis
- Congenital or postnatal infections
- Slow replication of bradyzoites in neurons (pseudocysts) during latency
- Headache, fever, confusion
- Multifocal necrotic encephalitis