Using LPS to model fatigue

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Disclosure
This certifies that I, JULIE LASSELIN, have no financial relationship that is relevant to the subject matter of this presentation.
Physiological, inflammation-related fatigue

Induced by e.g. exercise but also inflammation

Fatigue as an adaptive process
- Signal to rest
- Energy preservation
- Prevent injuries

Focus on energy-efficient actions

Inflammation-related fatigue: patients AND healthy individuals (infection)
Sickness behavior during acute inflammation (infection)

- Fatigue
- Changes in gait
- Motivational reorganization
  - Decreased motivation to e.g. play
  - Increased motivation to e.g. sleep
- Anxiety
- Negative mood
- Reduced appetite
- Social withdrawal
- Hyperalgesia
- Cognitive alterations
LPS model and sickness behavior

LPS (lipopolysaccharide) = bacterial endotoxin
LPS model: transient, dose-dependent, translational

Physiological response

Cytokine production

Fever

body temperature

hours

IL-6

IL-6

TNF-α

TNF-α

plac.

LPS low

LPS high

Dose:

iv 0.4-2.0 ng/kg bw

ip 100-830 μg/kg bw

Lasselin et al., 2020, Neurosc Biobeh Rev
Subjective fatigue after LPS

\[ \Delta \text{Fatigue} - \Delta \text{IL6} \]
\[ \beta(\text{SE}) = 0.592(0.178), p = 0.001 \]

\[ \Delta \text{Fatigue} - \Delta \text{TNF-\alpha} \]
\[ \beta(\text{SE}) = 0.785(0.173), p < 0.001 \]

Lasselin/Karshikoff et al., 2020, Brain, Behavior and Immunity
Effort/reward allocation after LPS

EEfRT (Effort Expenditure for Rewards Task, Treadway et al. 2009):

Low-effort/low-reward task

1$?

High-effort/High-reward task

1.2-4.2$?

WILLINGNESS TO EXPEND MORE EFFORT DEPENDING ON REWARD MAGNITUDE

Lasselin et al., 2017, Neuropsychopharmacology
Effort/reward allocation after LPS

EEfRT (Effort Expenditure for Rewards Task, Treadway et al. 2009):

- Low-effort/low-reward task: 30x / 7sec
  - 1$?
- High-effort/High-reward task: 100x / 21sec
  - 1.2-4.2$?

WILLINGNESS TO EXPEND MORE EFFORT DEPENDING ON PROBABILITY TO GET REWARD

Competition between need to rest and need for comfort?

Lasselin et al., 2017, Neuropsychopharmacology
Effort/reward allocation after LPS

Higher reward \(\rightarrow\) more effort
Similar in LPS and Placebo condition (similar liking)

Higher effort needed \(\rightarrow\) less effort
Stronger in LPS condition (reduced wanting)

Draper et al., 2017, Neuropsychopharmacology

BUT! Participants had to choose between making an effort to get a reward or do nothing (i.e. rest)
\(\rightarrow\) motivational drive to rest was stronger than to get a monetary reward

IN THIS CONTEXT
LPS model and inflammation-related fatigue

- Understanding physiological inflammation-related fatigue (dimensions, effect of context and type of rewards) and how it compares or differs to clinical fatigue
- Findings can be translated between animals and humans
- What make people more vulnerable or more resilient to develop inflammation-related fatigue
- Test therapies targeting the vulnerability factors

Potential therapeutic approaches

- Reducing psychological vulnerability
  - Cognitive behavioral therapies
  - Resilience training
- Restoring brain functions
  - Drugs targeting neurotransmitter metabolism (e.g., IDO inhibitors)
- Targeting inflammation
  - Anti-inflammatory drugs (e.g., COX inhibitors, cytokine antagonists, minocycline)
  - Nutritional interventions (e.g., omega-3 fatty acids)
  - Physical exercise

Endotoxin model

- Behavioral and affective changes
  - Depressive symptoms
  - Fatigue
  - Social interactions
  - Motivational changes
- Modulation of brain functions
  - Neuronal activity
  - Neurotransmitter metabolism
  - Neuroendocrine activation
- ↑ Central inflammation
  - Inflammatory markers (CSF)
  - Microglia activation
- ↑ Systemic inflammation
  - Inflammatory markers (blood)

Endotoxin administration (0.4 - 1.0 ng/kg)

Lasselin, et al. Mol Psychiatry 2020
Thank you

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