Teach the T cells: How Learning Can Shape Immunity

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Conditioned Taste Aversion

Acquisition (Learning)
Evocation (Memory)

Conditioned Response:
- Taste Aversion
- Immunological Changes

Conditioning Protocol

Groups                  CS-US      CS-US      CS      CS
                        Morning    Evening    Morning Evening

- Conditioned: Sac/CsA, Wat/PBS, Sac, Wat
- N.C.-Conditioned: Wat/CsA, Sac/PBS, Wat, Sac
- CsA-treated: Wat/CsA, Sac/PBS, Wat/CsA, Sac
- Untreated: Wat, Wat, Wat, Wat

Model of Action of Cyclosporine A

Cyclosporine A (CsA)
Calcineurin activity
IL-2
→ No T cell proliferation

Behaviorally Conditioned Response
Taste Aversion

Saccharin (g)

ASSAY

Behaviorally Conditioned Response
Taste Aversion

Saccharin (g)
Teach the T cells
Splenocyte Proliferation, Cytokine Production

**Splenocyte Proliferation**

- Conditioned
- Non Contingent Conditioned
- CsA-treated
- Unreated

**Interleukin-2**

- Conditioned
- Non Contingent Conditioned
- CsA-treated
- Unreated

Exton et al. 2002, *J Neuroimmunol*

Teach the T cells
Mechanisms

Central Processing

- Residual CsA
- Stress effect
- Splenic Nerve
- Noradrenaline
- β-Adrenergic receptors

Where?

Insular Cortex / Amygdala

When?

How?

Specificity?

Teach the T cells
Clinical Relevance

- Attenuation of Allergic Responses (DTH)
- Prolongation of Heart Allograft Survival
- Inhibition of Autoimmune Diseases (RA)

Teach the T Cells: Human Studies
Study Design

**CONDITIONING**

- CsA 2.5mg/kg (Sandimmun®) or Placebo

**RE-EXPOSITION**

- Placebo

DAYS

1 2 8 9

Psychological, Physiological, Neuroendocrine, Immune Parameters

Exton et al. 1998, *J Neuroimmunol*

von Hörsten et al. 1998, *J Neuroimmunol*

Exton et al. 1999, *Am J Physiol*

Exton et al. 2002, *J Neuroimmunol*

Pacheco-Lopez et al., 2005, *J Neurosci*

Doenlen et al. 2011, *Proc Biol Sci*

Pacheco-Lopez et al. 2009, *FASEB J*

Riether et al., 2010, *Brain Behav Immun*

Pacheco-Lopez et al., 2012, *Int J Neuropsychopharmacol*

Gudat et al. 2002, *FASEB J*
Behaviorally Conditioned Immunosuppression in Humans
Cyclosporine A Levels

Teach the T Cells: Human Studies
Cytokine mRNA Expression

Behaviorally Conditioned Immunosuppression in Humans
Interleukin-2 Production

Teach the T Cells: Human Studies
Preventing Extinction

Open Questions

- How much „conditioning is needed“?
- Can immune responses be induced by mere expectation?
- Predict Responder vs. Non-Responder of learned immune response
- The learned immune response can be re-produced
- Prevent extinction of learned immunosuppression

When does extinction of the learned immunosuppression occurs?
Teach the T Cells: Human Studies
Preventing Extinction

Albring et al. 2014, Clin Pharmacol Ther

Teach the T Cells: Human Studies
Preventing Extinction

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Teach the T Cells: Human Studies
Preventing Extinction

Teach the T Cells

Implementing Learning Protocols as Supportive Therapy in Immunopharmacological Treatment Strategies

- Reducing the dose of medication required
- Limiting unwanted drug side effects
- Maximizing therapeutic effects

Medication-ctrl
Conditioned-sub

Albring et al. 2014, Clin Pharmacol Ther