The Marmoset Monkey as Model for Neurological Disorders

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From Laboratory to Clinic

Scientific Principle

Laboratory

Disease models neuroscience:
- Parkinson
- Sleep
- Stress
- Alzheimer
- MS

Feasibility

Rodent

Confirmation

Preclinical validation

Safety & Efficacy

Monkeys

Clinical test

Clinic
MS Models: rhMOG induced models
Reduced spinal cord demyelination in EAE marmoset model with different diets

Yogurt-based diet (YBS) vs Water-based diet (WBS)

Kap YS et al, JI October 2018
Parkinson’s disease (PD), a progressive disease of the CNS

Motor disorder caused by degeneration of the dopamine neurons in the substantia nigra. Symptoms appear after already 60% of the dopamine neurons have disappeared.
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Motor disorder caused by degeneration of the dopamine neurons in the substantia nigra. Symptoms appear after already 60% of the dopamine neurons have disappeared.
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This delay is caused by compensatory pathways in the brain, in which the red nucleus (RN) is involved. This pathway is only active in human during the crawling period.

In rodents motor coordination is still organized by this pathway.

*Curr. Opin. Neurol.* **23**(4), 407-12
Parkinson’s disease: Pathogenesis

- Genetic models (5%)
  - Genetic Mutation (e.g. α-Synuclein and Parkin)
  - Inherited early onset PD

- Toxin induced models (95%)
  - Reactive oxygen species
  - Mitochondrial dysfunction
  - Degraded protein
  - Lewy bodies
  - Neurodegeneration
  - Apoptosis
  - Toxicity
  - Idiopathic PD
MPTP PD model byproduct in the synthesis of heroin

Clearly linked to a form of human parkinsonism: indistinguishable from idiopathic PD

In PD patients the RN is increased by 32%.
This suggests increased activity to compensate for the dysfunctional striato-thalamo-cortical pathway.

Colpan & Slavin 2010 *Parkins. Relat Disord.*
Sleep & Circadian rhythm: marker for prodromal stage of neurological disorders

Marmoset

Telemetric 24-h home cage activity

Human

“Normal”

Sleep Urge

Sleep Need

Sleep

Day 1

Day 2

Day 3

Day 4

Process C

Process S
Non-invasive behavioral test, telemetric neurophysiology and post-mortem assays to quantify effects of the disease progression and of a therapeutic intervention.

**Clinical symptoms**
- Clinical signs
  - Dyskinesia
  - Akinesia

**Motor function**
- Motor activity
- Hand-eye coordination
- Righting reflex

**Brain pathology**
- Dopamine levels
- Histology (TH staining)
- Brain imaging

**Non-motor symptoms**
- Sleep disorders
- Cognitive decline

**Test Methods**
Stress related emotional memory

Retrospective studies in humans are difficult to perform and most studies fail to control for stress event, limiting the results of these studies.

⇒ Controlled animal research is needed that optimally uses cross-species characteristics by integration of the mechanistic disturbance with symptoms, which can be applied to animals and humans alike.
Why the marmoset monkey for stress research

Anatomical

- The structural plasticity in the amygdala in the marmoset is in line with other non-human primates and humans (Marlatt et al., 2011).
- The evolutionary anatomical and functional organization of the prefrontal cortex is well conserved in primate species including the marmoset monkey.

Behavioural and hormonal

- Monkeys are diurnal and the sleep stages are similar to those in humans; Rodents have a fragmented sleep during the day.
- Sleep affects hormones involved in the circadian rhythm, such as cortisol. In human and marmoset cortisol increases in the morning, in rodents in the evening.
- In contrast to this fluctuation, melatonin levels in all species increase in the evening, which is related to sleepiness in humans and monkeys and to wakefulness in rodents.
Physical stress paradigms make use of the classical conditioning procedure:
- it relates an aversive stimulus to an environment factor
- (shock-context with situational memories)
- Such as the passive avoidance test
The time of stress exposure is known and the time of treatment can be well defined.
**Week 2**

**Re-consolidation**

- **Ketamine 0.5mg/kg**
- **Saline**

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Biomedical Primate Research Centre
Committed to health research and alternatives
Amyloid-beta model for AD in the marmoset

Amyloidosis is inducible in the marmoset and activated by inflammation

Marmosets spontaneously develop Aβ aggregates during aging with a distribution and chemical composition similar to those found in human

β-amyloidosis is a transmissible process from patients to primates and the addition accelerate the process of amyloidosis in primates

(Baker et al. 1993; Maclean et al.2000; Ridley et al.2006; Geula et al.2002).

High levels of IL-1β, IL-6 & TNF-α are found in brains of PD and AD patients. Anti-inflammatory medication reduces the risk of AD.

• NSAIDs in Rheumatoid arthritis patients: lower incidence of AD (Dinkel, K. et al. (2004) PNAS).
<table>
<thead>
<tr>
<th>Induction</th>
<th>IS</th>
<th>Substance injected</th>
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<tbody>
<tr>
<td>1 LPS/PBS</td>
<td></td>
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<tr>
<td>2 LPS/PBS</td>
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<tr>
<td>3 LPS/PBS</td>
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</tr>
<tr>
<td>4 human Aβ + LPS/PBS</td>
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<tr>
<td>5 artificial Aβ + LPS/PBS</td>
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<tr>
<td>6 artificial Aβ + LPS/PBS</td>
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2/3 of the LPS+Aβ injected marmosets developed plaque progression.

None of the PBS+Aβ injected marmosets showed any plaques in a 5-month period.
Conclusions

Brain Related Disorders can be Induced or appears Spontaneously in the Marmoset monkey.

✓ MPTP model for Parkinson; A-beta model for Alzheimer; stress model
✓ Similarity of circadian rhythm and sleep architecture between marmosets and human

Non-invasive (behavioural) Test Methods are Available.

✓ Activity, motor function, cognition, clinical signs
✓ Telemetry gives the opportunity to measure EEG in free moving animals preventing stress caused by immobilization due to wires
✓ Disease progression or the effect of a treatment can be followed during a long period of time in the same animal strengthen the 3-Rs policy