





# Fibromyalgia – state of the art

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# Pain mechanisms?





# Pathophysiology - central



**Dysfunction of EIH<sup>4</sup>** 



Reduced opioid binding potential (rACC)<sup>5</sup>

Before T

During T

■ Following T



<sup>1</sup>Kosek et al., Pain 1995, <sup>2</sup>1996, <sup>3</sup>Kosek et al. Pain 1997, <sup>4</sup>Lannersten and Kosek, Pain 2010. <sup>5</sup>Schrepf et al., Pain 2017,

## fMRI: FM patients compared to HC



P50: 50mm VAS

FM HC

P50: FM < HC, p < 0.002

FM patients had decreased activity in brain regions implicated in descending pain inhibitory pathways during nociceptive stimulation<sup>1</sup>

Thumbnail 
$$HC_{pain-sensory} - FM_{pain-sensory}$$
 (n = 32)



Rostral anterior cingulate cortex (rACC)



FM patients had reduced functional connectivity between rACC and amygdala and rACC and brainstem/PAG<sup>2</sup> (n = 42)

Thalamus

PAG = periaqueductal grey fMRI = functional magnetic resonance imaging

<sup>1</sup>Jensen et al. Pain 2009, <sup>2</sup>Jensen et al. Mol Pain 2012

FM patients had reduced brain volumes, cortical thickness and functional connectivity of rACC compared to controls





N = 26 FM, 13 HC

Jensen et al. Arthrit & Rheum 2013

# Segregated mechanisms for pain and negative affect in fibromyalgia

- Ratings of depression/anxiety were not related to:
  - Clinical pain intensity
  - Pressure pain sensitivity
  - Cerebral processing of pressure pain

 High ratings of depression/anxiety were related to low health esteem.



Main effect of cerebral processing of pressure pain, not influenced by mood

N = 83

#### Jensen et al., Arthritis & Rheum 2010

# Conclusions

Figure from: Wiech et al. Trends Cogn Sci, 2008



- FM patients have a dysfunction of descending pain inhibition, linked to opioid mechanisms<sup>1,2,3</sup>
- There was an overlap between functional and structural changes in the brain in FM patients<sup>4</sup>
- Longer pain duration was related to smaller brain volumes<sup>4</sup>
- Ratings of depression/anxiety were not related to pain symptoms or cerebral pain processing indicating segregated mechanisms<sup>5</sup>

<sup>1</sup>Jensen et al. Pain 2009, <sup>2</sup>Jensen et al. Molecular Pain 2012, <sup>3</sup>Schrepf et al. Pain 2016, <sup>4</sup>Jensen et al. Arthrit & Rheum 2013, <sup>5</sup>Jensen et al., Arthritis & Rheum 2010



### Microneurography: Spontansous C fiber activity and increased excitability in fibromyalgia patients



Serra et al., Ann Neurol 2014

## <u>Skin punch biopsy:</u> reduced intraepidermal nerve fibre density (IENFD) in fibromyalgia



Evdokimov et al. Ann Neurol 2019

## Reduced intraepidermal nerve fibre density (IENFD) was related to more severe fibromyalgia symptoms



FM patients with distal and proximal reductions in IENFD compared to FM patients with normal IENFD rated:

- Higher pain intensity
- More severe FM symptoms (higher FIQ)
- More anxiety (higher STAI-T)
- They also had higher BMI

Evdokimov et al. Ann Neurol 2019



### Increased CSF and serum concentrations of IL-8 in FM

CSF: P = 0.001

Serum: P = 0.02



N = 15 FM, 15 NINS, 15 HC

#### Kadetoff et al. J Neuroimmunology 2012

# Neuroinflammation in fibromyagia



Bäckryd et al. J Pain Res 2017



#### CSF IL-8

Released by activated astrocytes<sup>1</sup> Activate microglia<sup>1</sup> Neuronal excitability ↑<sup>2</sup>

**CX3CL1 (Fractalkine)** Neuron to microglia signalling<sup>2</sup>



#### Immune system



**Nervous system** 

<sup>1</sup>Koyama et al. J Neuroinfl 2013; <sup>2</sup>Zhang et al. Cell Mol Life Sci, 2017;

# Induced systemic inflammation (LPS) affects pain sensitivity and conditioned pain modulation (CPM) more in women than men



#### Increased pain sensitivity

Reduced descending pain inhibition (CPM)



#### Increased release of IL-8



N = 52LPS = lipopolysaccharide

Karshikoff et al. Brain Beh Immunity, 2015, 2016

# Decreased pain related activation of rACC in women following LPS injection



#### Karshikoff et al. Brain Beh Immunity, 2016

#### Microglia activation ([<sup>11</sup>C]PBR28 (TSPO) PET) 3 h following i.v. LPS injection (1.0 ng/kg) (n =8)



#### Sandiego et al. PNAS 2015

#### Increased glia cell activation in fibromyalgia PET: TSPO ligand ([<sup>11</sup>C]PBR28)

Voxelwise group differences in [11C]PBR28 SUVR

FM n = 31, HC n = 27 Data adjusted for genotype and injected dose



Assoc. Prof Marco Loggia, Harvard Medical School



PET = positron emission tomography TSPO = translocator protein

Albrecht, Forsberg et al. Brain Behav Immun 2018

#### Increased glia cell activation in FM was associated with increased fatigue [<sup>11</sup>C]PBR28 SUVR





Assoc. Prof Marco Loggia, Harvard Medical School

aMCC = anterior mid cingulate cortex pMCC = posterior mid cingulate cortex

Albrecht, Forsberg et al. Brain Behav Immun 2018

### No evidence of astrocyte activation

No group differences in  $[^{11}C]$ - $_L$ -deprenyl-D<sub>2</sub> binding  $\lambda k_3$  differences in (p>0.53 uncorrected)





These results indicate microglial, rather than astrocytic, activation, but need to be reproduced (n = 22).

Albrecht, Forsberg et al. Brain Behav Immun 2018



### Human IgG antibodies injected in mice



Goebel et al. BioRxiv 2019, under review Nature Neuroscience

### IgG from FM patients induced hypersensitivity to mechanical and cold pain in mice







Goebel et al. BioRxiv 2019, under review Nature Neuroscience

### FM IgG accumulates in the DRG, binds to satellite glial cells and activates them



IgG from FM patients, but not HC, accumulated in satellite glia cells in the dorsal root ganglia 14 days after injection in mice



Increased satellite glia cell activity (GFAP) in DRGs from mice treated with FM IgG

Goebel et al. BioRxiv 2019, under review Nature Neuroscience

# What are satellite glia cells?





Illustration from Wang et al. Cell Biol Internat. 2019



Illustration from Int J Oral Sci 2019

Illustration from Goebel, J Clin Immunol 2010

### IgG from FM patients induced increased response of rodent C and A-delta fibres to mechanical and cold stimuli

Mechanosensitive A-delta fibres

Cold sensitive A fibres

Mechanosensitive C fibres



Goebel et al. BioRxiv 2019, under review Nature Medicine

## FMS IgG induced reduced intraepidermal nerve fibre density (IENFD) in mice



Under review, Nature Medicine, courtesy of Camilla Svensson

# Summary

- Hypersensitivity to mechanical and cold stimuli
- Increased excitability of peripheral nociceptive afferents
- Reduced intraepidermal nerve fibre density





# FM as an autoimmune disease? Antigens?





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#### Thank you for your attention



# What are satellite glia cells?



