TOBeATPAIN e-seminar

Central sensitization in Rheumatic diseases

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Introduction

Central sensitization can be characterized by an augmented response of the central nervous system (CNS) in response to pain. Increased synaptic efficacy and/or dysfunction in the descending pain inhibition pathway has been shown to be a cause.

Rheumatoid arthritis (RA) is characterized by joint inflammation and pain. However, after overt joint inflammation resolution, these patients have refractive pain. This made researchers wonder if there is a central sensitization component in this disease.

The cardinal symptom of *Fibromyalgia* (FM) is chronic widespread pain. Furthermore, other symptoms that these patients can show are cognitive dysfunction, sleep disturbance, tenderness and fatigue. FM is a comorbidity of RA in around 13-25% (1) of the cases. Other RA patients report FM symptoms that can be called *FMness* (2).

Patients with these diseases therefore have a decreased quality of life and limited ability to lead productive lives due to chronic pain. Chronic pain is a societal challenge which makes research in the chronicity of pain extremely relevant.

Paper 1

Silvia Fanton (ESR3), supervised by prof. Eva Kosek and Zerina Kurtovic (ESR5) supervised by prof. Camilla Svensson each presented a paper that contribute to our current understanding of central sensitization in rheumatic diseases.

Silvia Fanton presented "Neurobiologic features of Fibromyalgia are also present among Rheumatoid Arthritis patients" - Basu *et al.*, 2018, *Arthritis and Rheumatology,* which is a study on central sensitization through neuroimaging techniques to investigate the correlation of higher connectivity of dorsal attention network (DAN), sensorimotor network (SMN), salience network (SN) and the insular cortex (3) with FMness.

54 patients were included with RA and a high FMness score. Upon inclusion c-reactive protein levels, as well as disease activity, fatigue, pain severity, sleep disturbance and depression score were analyzed.

Results showed a positive correlation of the connectivity of the default mode network and insula with patients with high scores of FMness in RA patients. Moreover, associations with fatigue, sleep disturbance and disease activity were also found. In sum, the results showed a central sensitization component in these patients that may be a marker of this process. This may show a dysfunctional descending pain inhibition pathway that can be associated with the chronic pain.

Paper 2

Zerina Kurtovic presented "Sex-dependent role of microglia in disulfide HMGB-1-mediated mechanical hypersensitivity" - Agalave *et al*, 2020, *Pain*, a paper with a pre-clinical focus on chronic pain and HMGB1.

HMGB1 is a protein with various roles and it's expressed by a number of immune cells. However, this paper focused on disulphide HMGB1 (ds-HMGB1), the oxidation state of HMGB1 that promotes cytokine activity (4). It has been shown that this protein binds to TLR4, activating glia in spinal cord and promoting hypersensitivity in mice (5). In addition, it's stressed that the distinct role of certain proteins in the immune system react differently in males and females and influences the mechanism of hypersensitivity differently.

The aim of this study was to understand if ds-HMGB1 generates pain through microglia in a sex-dependant manner.

The results showed an increase of microglia activation with the injection of ds-HMGB1 in the spinal cord of females and males, but this activation lead to a higher production of cytokines in males than females. All showed hypersensitivity upon ds-HMGB1 injection. Nonetheless, after knock-out of TLR4 in myeloid cells, ds-HMGB1 induces pain in female mice that is not seen in male mice and after treatment with minocycline, a microglia inhibitor, pain persisted in females in contrast to males.

The paper also included a proteome profile analysis showing A1AT to be associated with a potential protective effect of pain. A1AT was found to be upregulated in male mice upon injection of ds-HMGB1 and minocycline.

The authors also found that PAR2 is significantly lower in both sexes in comparison to vehicles and that this protein attenuates pain in females and males.

To conclude ds-HMGB1 microglial activity may contribute to central sensitization, predominantly in males.

It is important to underline the relevance of such study because pain may be mediated differently in both sexes and this needs to be taken into account when developing treatment to female and male patients.

Conclusion

After each presentation there was a fruitful discussion by the speakers and audience. The seminar contributed to the general knowledge of the attendees and early stage researchers who had the opportunity to develop their skills, by preparing the presentation of a very relevant topic for their projects.

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References

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(3) Power, J.D. (2011). Neuron.
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(5) Agalave *et al.* (2014). Pain.