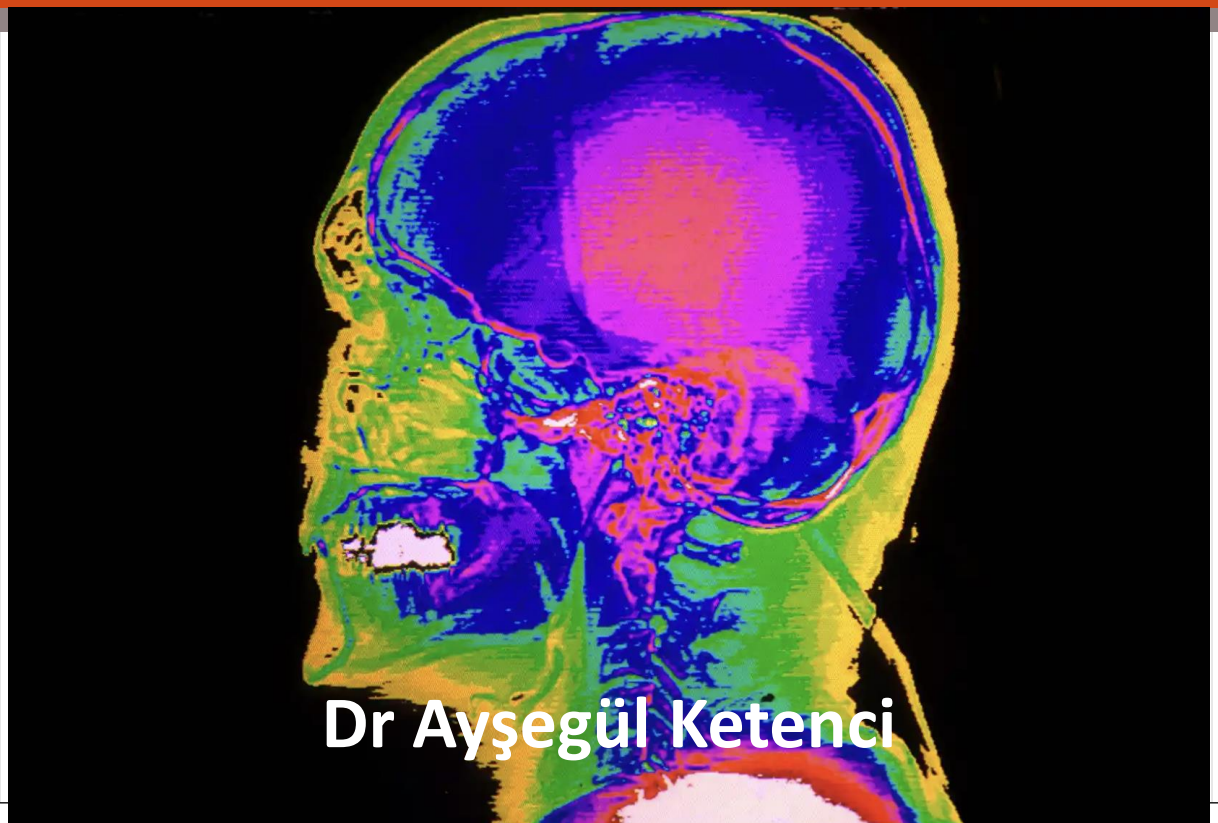
# Santral Ağrı Mekanizmaları



Dr Ayşegül Ketenci

# Romatizmal hastalıklar&Ağrı

- İnflamatuvar romatolojik hastalıklarda ağrı kompleks
- Uygun inflamasyon kontroluna rağmen hastaların %50'den fazlası hala klinik olarak anlamlı ağrılı
- Santral sensitizasyon-Hassas eklem??
- FMS, RA hastalarında %17-25

**Arthritis 2015 2015 434109**
**Arthritis Rheumatol 2018 Jul 70 (07) 1000-07**
**Scand J Rheumatol 2021 Sep 1;1-10**

**Pain in rheumatoid arthritis: a seven-year follow-up study of pain distribution and factors associated with transition from and to chronic widespread pain**

MLE Andersson[1,2], B Svensson[1], and S Bergman[1,2,3]

- RA hastaların %29'u iyi klinik cevaba rağmen ağrılı
- Ağrılı hastaların %30'u ağrıyı «kabul edilemez» olarak tanımlıyor
- RA'de inflamasyon nosiplastik ağrıyı tetikleyen santral ve periferik sensitizasyon ile birlikte gidiyor
- İlerleyen dönemlerde yapısal değişiklik katkıda bulunuyor

**Scand J Rheumatol . 2021 Sep 1;1-10**

Current Pain and Headache Reports (2021) 25:59
https://doi.org/10.1007/s11916-021-00973-0

NEUROPATHIC PAIN (A ABD-ELSAYED, SECTION EDITOR)

# Chronic Pain in Patients with Rheumatoid Arthritis

| Mechanisms of chronic pain in RA | |
|---|---|
| Inflammatory pain | Driven by local and systemic cytokine effects. Locally, cytokines recruit inflammatory cells that cause pain and swelling. Systemically, cytokines modulate central pain processing through unclear mechanisms. |
| Structural pain | Increased nociceptive pain at inflamed joint surfaces and non-joint sites. |
| Central and peripheral sensitization | Increased neuronal recruitment peripherally through immune complex-mediated activation of neurons and centrally through unclear mechanisms. |
| Secondary pain syndromes | Comorbid OA and FM can add to chronic pain in RA. |
| Psychological susceptibilities | Unclear mechanisms link psychological comorbidities and RA. Depression is independently associated with the central processing of pain. |

# Is central sensitization an important determinant of functional disability in patients with chronic inflammatory arthritides?

*Ther Adv Musculoskel Dis*

2021, Vol. 13: 1–11

DOI: 10.1177/1759720X21993252



**Results:** We enrolled 150 patients with inflammatory arthritides (78 PsA and 72 RA). Prevalence of CS was observed in 35.3% of the overall sample (29% in RA, 42.9% in PsA). Binary logistic regressions showed a strong, independent and linear association between functional disability and CS in both PsA and RA patients. The strength of this association was greater in PsA than in RA.

**Conclusion:** CS is an important determinant of functional disability in patients with chronic inflammatory arthritides. PsA appeared to be more vulnerable to CS. In addition, in the presence of CS, DAPSA did not adequately capture the occurrence of functional disability. Therefore, special attention should be paid to PsA patients, in whom the concomitant diagnosis of CS should be routinely ruled out.

# Pain in rheumatoid arthritis: a seven-year follow-up study of pain distribution and factors associated with transition from and to chronic widespread pain

MLE Andersson[1,2], B Svensson[1], and S Bergman[1,2,3]

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rheumatoid arthritis (RA).

**Method:** Two postal questionnaires were sent to patients included in the BARFOT (Better Anti-Rheumatic Pharmacotherapy) study, the first in 2010 and the second in 2017. The questionnaires assessed pain, number of tender and swollen joints, functional disability, health-related quality of life (HRQoL), pharmacological treatment, lifestyle factors, and patient-reported body mass index (BMI). The responders to both questionnaires were divided into three groups according to the reported pain duration and distribution: patients having no chronic pain (NCP), chronic regional pain (CRP), and CWP.

**Results:** In all, 953 patients answered the questionnaires at both time-points. One-third (324) of the patients reported CWP in 2010, and 140 (43%) of the patients had transition to NCP or CRP in 2017. In multivariate logistic regression models, adjusting for age, gender, and disease duration, transition from CWP was associated with normal BMI, fewer tender joints, less pain, less fatigue, fewer pain regions, less disability, better HRQoL, and biologic treatment. In 2010, 628 patients reported NCP or CRP, whereas 114 of them reported CWP in 2017. Transition to CWP was associated with female gender, obesity, more tender and swollen joints, higher pain-related variables, worse disability, and worse HRQoL.

**Conclusion:** There are modifiable factors associated with transitions from and to CWP that could be identified. Paying attention to these factors could improve pain treatment in the management of RA.

ARTICLE HISTORY

Lee et al. Arthritis Res Ther (2021) 23:278
https://doi.org/10.1186/s13075-021-02653-1

Arthritis Research & Therapy

RESEARCH ARTICLE Open Access

# Baseline predictors of remission, pain and fatigue in rheumatoid arthritis: the TITRATE trial


## Abstract

**Background:** Clinical trials show intensive treatment to induce remission is effective in patients with highly active rheumatoid arthritis (RA). The TITRATE trial showed that the benefits of intensive treatment also extend to moderately active RA. However, many patients failed to achieve remission or show improvements in pain and fatigue. We investigated whether baseline predictors could identify treatment non-responders.

**Methods:** The impact of obesity, depression, anxiety and illness perception on RA outcomes, including disease activity, remission, pain and fatigue were determined using a pre-planned secondary analysis of the TITRATE trial data.

**Results:** Body mass index was associated with disease activity levels and remission: obese patients had a higher overall disease activity and fewer obese patients achieved remission. Intensive management was not associated with increased remission in these patients. Obesity was also associated with increased overall pain and fatigue. Anxiety, depression and health perceptions had no discernible impact on disease activity but were associated with high levels of pain and fatigue. There was a strong association between anxiety and high pain scores; and between depression and high fatigue scores; and health perception was strongly related to both. None of the predictors had an important impact on pain and fatigue reduction in cross-sectional analysis.

**Conclusions:** Disease activity is higher in obese patients and they have fewer remissions over 12 months. Anxiety, depression and health perceptions were associated with higher pain and fatigue scores. Intensive management strategies need to account for these baseline features as they impact significantly on clinical and psychological outcomes.

**Running head:** Pain sensitization as a mediator between sleep and pain

**Title:** Pain sensitization as a potential mediator of the relationship between sleep disturbance and subsequent pain in rheumatoid arthritis

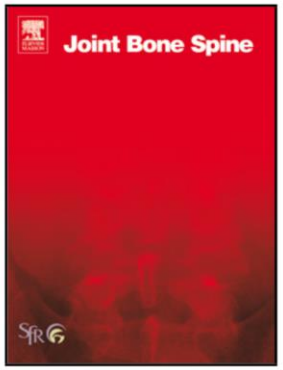
Jing Song, MS [1], Lutfiyya N. Muhammad, PhD[1], Tuhina Neogi, MD, PhD[2], Dorothy D. Dunlop, PhD[1], Alyssa Wohlfahrt, MS[3], Marcy B. Bolster, MD[4], Clifton O. Bingham III, MD[5], Daniel J. Clauw, MD[6], Wendy Marder, MD[6], Yvonne C. Lee, MD, MMSc [1]

[1] Northwestern University Feinberg School of Medicine, Chicago, IL

- Uyku bozukluğu, eklem ağrısı dışında ağrı duyarlılaşmasının belirteci olabilir.

**Arthritis Care Res (Hoboken) 2022 Mar 3**

# Journal Pre-proof




Assessing central sensitization with quantitative sensory testing in inflammatory rheumatic diseases: a systematic review

Anne-Priscille Trouvin Nadine Attal Serge Perrot

PII: S1297-319X(22)00058-6

DOI: https://doi.org/doi:10.1016/j.jbspin.2022.105399

Reference: BONSOI 105399

- Results show decreased pain thresholds, especially to pressure pain at pain sites and at sites remote from the inflammed joints or muscles, in some patients with rheumatoid arthritis and spondyloarthritis in favor of diffuse mechanical allodynia.

**Joint Bone Spine 2022 Apr 30;105399**

# RA ve Ağrı

- Ağrının santral işlenmesi
  - Spinal ve supraspinal düzeyde değişim
  - Çıkan ağrı yolaklarında bağlantılarda artma, inen kontrol sisteminde bağlantılarda azalma
  - Kortikal incelme

IL-1β, IL-6, TNF alfa'ya spinal maruziyet-allodini ve hiperaljezi

**Nat Rev Rheumatol 2014 Oct 10 (10) 0581-92**
**Clin Exp Rheumatol 2017 Sep-Oct 35 S 107 (05) 0094-101**

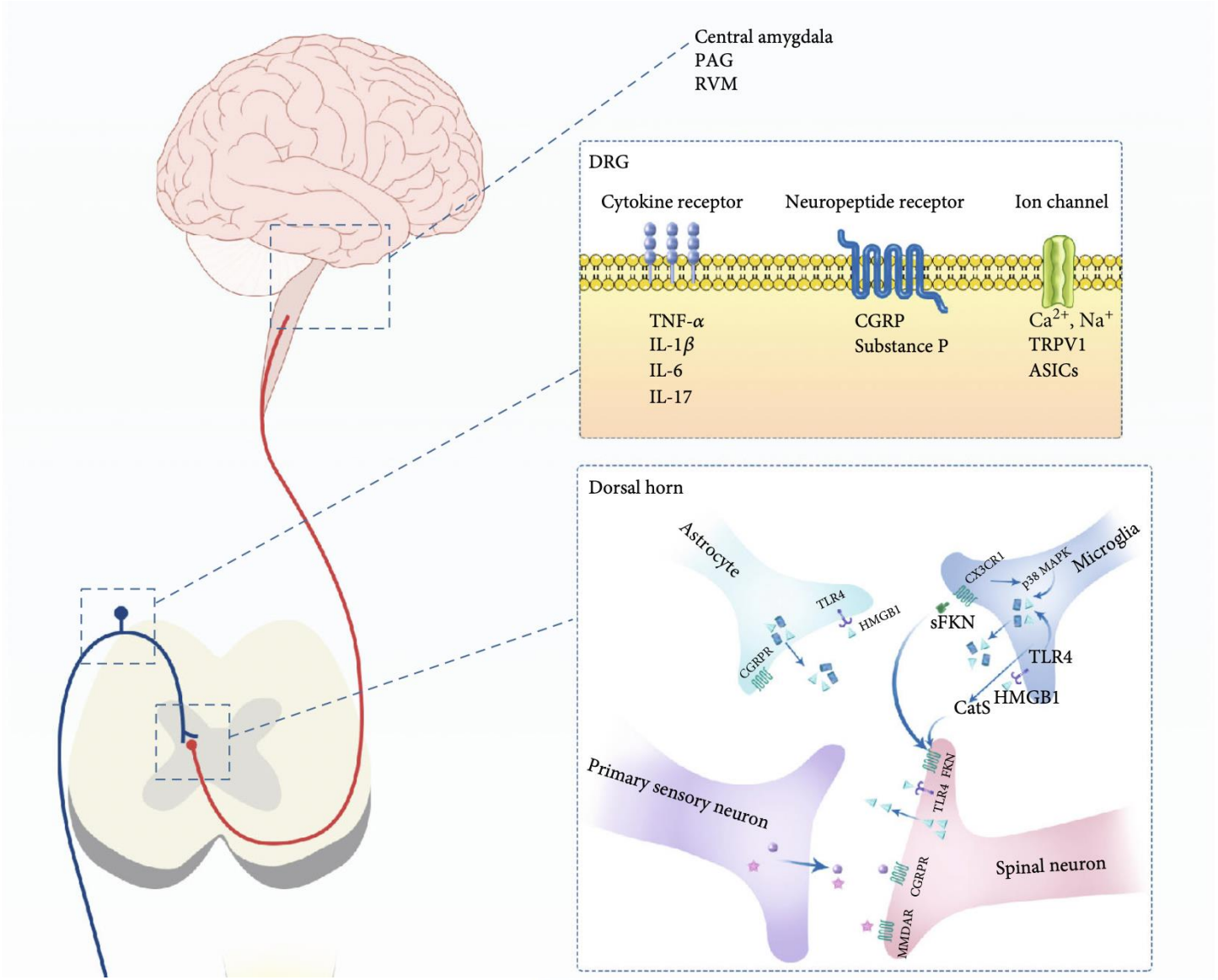
# Santral sensitizasyon

- Glutamat aracılı NM… …ı ile akut faz

Allodini, hiperaljezi, **temporal sumasyon** ve dermatom dışı yayılan hiperaljezi- **sekonder hiperaljezi**

- Kronik dönemde ağrı ile ilgili peptidlerin transkripsiyonu ve spinal mikroglia'nın aktiflenmesi

**Curr Osteoporos Rep 2018 16 (05) 0603-10**


Central amygdala
PAG
RVM
DRG
Cytokine receptor
Neuropeptide receptor
Ion channel
TNF-α
IL-1β
IL-6
IL-17
CGRP
Substance P
Ca2+, Na+
TRPV1
ASICs
Dorsal horn
Astrocyte
TLR4
HMGB1
CGRPR
Microglia
CX3CR1
p38 MAPK
sFKN
TLR4
CatS
HMGB1
Primary sensory neuron
FKN
TLR4
Spinal neuron
CGRPR
MMDAR

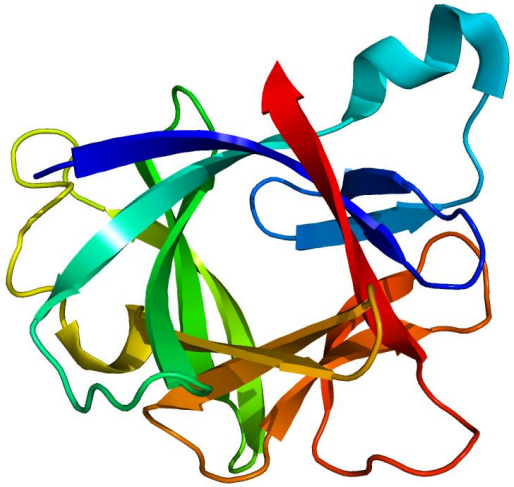
A

| Cytokine | RA | PsA | Effect on Pain |
|---|---|---|---|
| IFN-α/β | + | - | - |
| IFN-γ | - | + | - |
| IL-1 | + | + | + |
| IL-2 | - | + | - |
| IL-6 | + | + | + |
| IL-7 | + | + | - |
| IL-10 | + | + | - |
| IL-12 | + | + | - |
| IL-15 | + | + | - |
| IL-17 | + | + | + |
| IL-18 | + | + | - |
| IL-21 | + | - | - |
| IL-22 | - | + | - |
| IL-23 | + | + | ± |
| GM-CSF | + | - | - |
| TGF-β | + | - | - |
| TNF-α | + | + | - |

1;39(3)-668-75

# İnflamatuvar hastalıklar ve IL-1β

- Ağrı iletiminde IL-1β'nın önemi, DKG'da IL-1R'nin varlığının gösterilmesi ile anlaşılmıştır
- Hayvan modellerinde IL-1β'nın inhibe edilmesi, TRPV1 reseptörlerinin aktivitesini azaltarak termal hiperaljeziyi düzeltir
- Hayvan modellerinde C liflerinin mekanosensitivitesini arttırırken, A**δ** liflerini azaltır

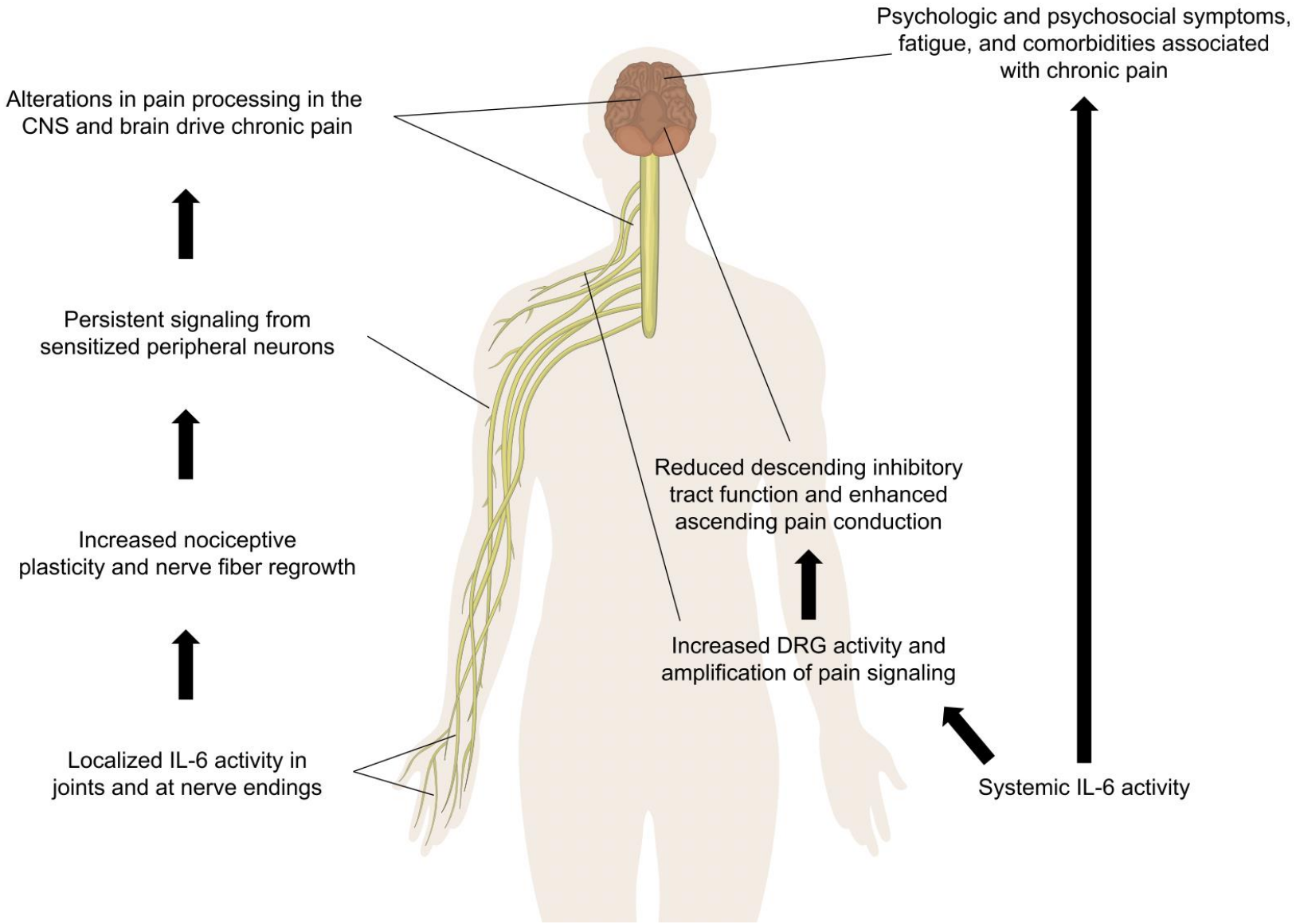


**Clin Exp Rheumatol. May-Jun 2021;39(3)-668-75**

# İnflamatuvar hastalıklar ve IL-6

- DKG ve spinal kord glial hücrelerinde reseptörleri mevcut
- IL-23, IL-17A ve IL-18 ile koordineli çalışır, siyatik sinir yaralanması ağrı modelinde bu sitokinleri arttırdığı gösterilmiştir
- Parkinson, MS gibi hastalıklarının ağrısında SSS'de yüksek oranda görülmüştür (inflamasyondan bağımsız ağrı modülatörü)

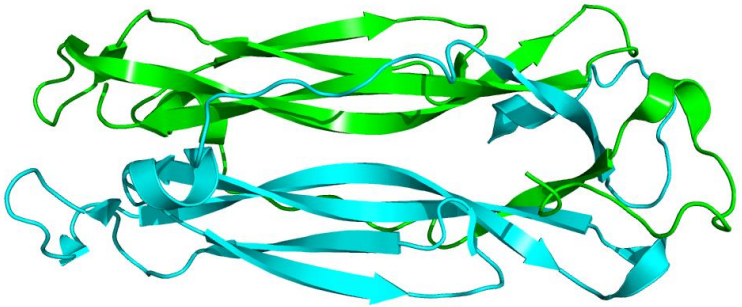
**Clin Exp Rheumatol May-Jun 2021;39(3)-668-75**
**Open Access Rheumatol 2021 Mar 5;13-31-43**




**Open Access Rheumatol 2021 Mar 5;13-31-43**

# İnflamatuvar hastalıklar ve IL-23/IL-17

- IL-17, nöroinflamasyon ve ağrı hiper sensitivitesinde rol alır
- DKG'da reseptörü gösterilmiş
- IL-23, IL-17'yi modüle ederek etki eder



**Clin Exp Rheumatol. May-Jun 2021;39(3)-668-75**

Rheumatologists are aware of other conditions that may be comorbid with RA (eg, osteoporosis, cardiovascular disease), but they do not typically think of CNS involvement as part of the comorbid process of RA. Evidence seems to suggest this should change and that we should be cognizant of nervous system involvement as a fairly common and major target organ that merits separate consideration when treating patients.

**Teşekkürler....**