Paracetamol Self-Medication and Medication-Overuse Headache

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Introduction

Most commonly self-used NSAID to treat headache globally: Ibuprophen, Aspirin, Paracetamol (the most used in Europe).

General unawareness of the risk of developing MOH.
The term MOH first appeared in 2004.

Objective: make a bibliography review in order to establish how paracetamol overuse can cause MOH and to investigate the pharmacological and physiopathological mechanisms involved in MOH development.

Methods: bibliographical search in *PubMed* and *ScienceDirect*, specially scientific papers and reviews.

Abbreviations used:
- Central sensitisation (CS)
- Central Nervous System (CNS)
- Cyclooxygenase (COX)
- Cytoplasmic (CY)
- Long-term potentiation (LTP)
- Medication-Overuse Headache (MOH)
- Non-steroidal anti-inflammatory drugs (NSAID)
- Over-the-counter (OTC)
- Periaqueductal Grey Matter (PAG)
- Serotonin (5-HT)

Paracetamol

- OTC NSAID.
- Analgesic and antipyretic effects, not anti-inflammatory.
- Central effect (ability to penetrate into the brain), inhibition of COX-3.
- Mechanisms contributing to its antinociception effect:

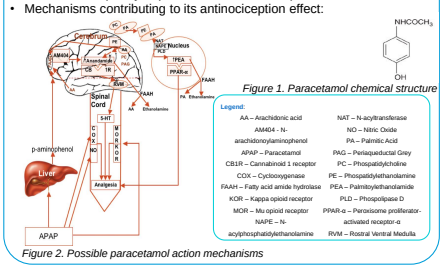


Figure 2. Possible paracetamol action mechanisms

Figure 1. Paracetamol chemical structure

MOH

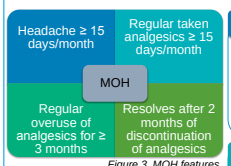


Figure 3. MOH features

Only individuals with a primary headache develop MOH.

Epidemiology:
- 1,5% global population (2,6% ♀, 0,19 ♂).
- Spain: 1,41% population (2,6♀ and 0,2%♂).

High risk of developing MOH
- **Paracetamol**
- Aspirin
- Opioids
- Ergotamine
- Butalbital
- Caffeine combinations

Medium risk of developing MOH
- Triptans
- Short-acting NSAIDs

Low risk of developing MOH
- Long-acting NSAIDs
- Dihydroergotamine
- Tramadol
- Neuroleptics

MOH Aeotiology

Paracetamol as the cause

Involvement of serotonin system

Acute paracetamol administration
- Extracellular 5-HT levels increase.
- Maximal number of cortical 5-HT$_{2A}$ receptors decrease.
- Down-regulation of postsynaptics 5-HT$_{2A}$ receptors: ↓binding-sites.
- Descending serotoninergic pathways inhibit nociceptive stimuli by:
  - Hyperpolarization of projection neurons or central terminalis of primary afferent fibers.
  - Excitation of inhibitory interneurons containing GABA and enkephalin.

Chronic paracetamol administration
- Extracellular 5-HT levels decrease.
- 5-HT$_{2A}$ receptors density increase.
- Up-regulation of 5-HT$_{2A}$ receptors: ↑ binding sites.
- 5-HT$_{2A}$ activation → ↑ COX-2 (nociceptive messenger).
- Loss of analgesic efficacy, restoration of sensitivity, hyperalgesia, potentiation of nociceptive transmission.

Figure 4. Paracetamol effects in acute and chronic administration

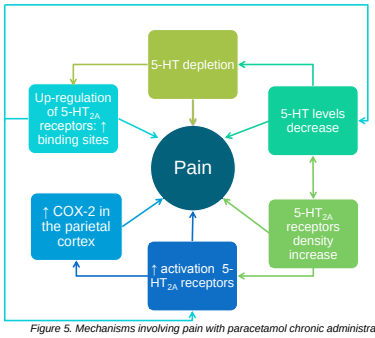


Figure 5. Mechanisms involving pain with paracetamol chronic administration

Cellular adaptation in the brain

Chronic exposure causes an impairment of the modulatory neurons in the CNS (abnormal membrane transduction).

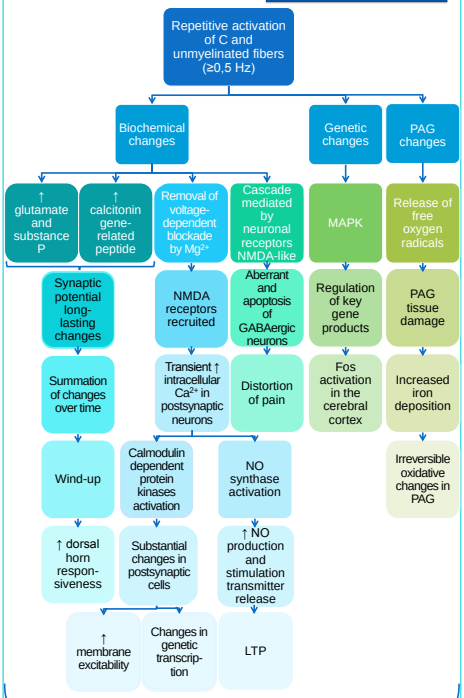
Glucose metabolism alteration

Increased glucose metabolism in insula (pain experience).

Repetitive activation of nociceptive pathways

Central Sensitisation
- Nociceptors become more sensible
- Enlargement of the receptive fields
- Activation of previously silent nociceptors
- Biological and functional changes in the trigeminal nucleus
- Changes in PAG

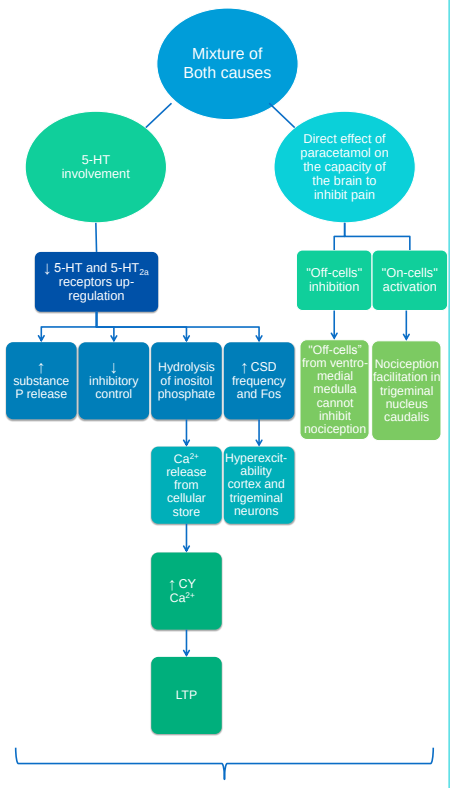
→
- Response to non-noxious stimuli
- Increase in responsiveness to suprathreshold stimulation
- Expansion of pain area
- Recruitment of nociceptive neurons from higher levels
- Hyperalgesia
- Allodynia



Central Sensitisation

Figure 6. Mechanisms involving CS due to a repetitive activation of nociceptive pathways

Paracetamol and Sensitisation



Nociception increase and Central Sensitisation

Figure 7. Mechanisms involving CS due to chronic paracetamol administration

Paracetamol addiction (Hypoteses)
- Compulsive reward-seeking.
- Behaviioural sensitisation induced by drug administration in addiction.
- Dopamine involvement: pain and reward.

Conclusions

- In general, type headache diagnosis is difficult, especially with MOH, which is a recent-discovered pathology. That is the reason why physiopathological and pharmacological mechanisms involved in MOH are little known. However, this topic is under investigation and some important findings and interesting hypotheses have been discovered.
- There are two principal aetiological groups of MOH that are interconnected; they imply reiterated use of paracetamol and repetitive activation of nociceptive pathways. This activation is basically due to treatment of the pain symptoms but not the real cause or origin of headache.
- One of the principal mechanisms involved in MOH development lies in the integrity of serotonin system, either with serotonin or its 5-HT$_{2A}$ receptor. It is curious how an acute intake of paracetamol can lead to analgesia whereas a chronic intake leads to the opposite: pain.
- Another of the main mechanisms are central sensitisation and cellular changes that suffer nociceptive neurons, either by repetitive activation of these pathways or the involvement of paracetamol in central sensitisation.