

RESUMEN

A large number of chemical mediators and neurotransmitters are involved in the processing of nociceptive information, both in peripheral sites and in the central nervous system. The final sensation of pain depends on the interaction among these neuromodulators. Chemical mediators implicated in the nociceptive system can be pooled in two groups: pronociceptive substances, which facilitate the transmission of the nociceptive message and the development of pain, and analgesic or antinociceptive substances, which difficult the transmission of the nociceptive information and, therefore, reduce or eliminate pain. Analgesia can be reached through the activation of inhibitory systems or/and by the blockage of excitatory systems.

Among the systems involved in nociception, we have studied the analgesic actions of medetomidine (MED), an α_2 -adrenergic agonist, and the pronociceptive actions of all-*trans* retinoic acid (ATRA), an active metabolite of vitamin A, as well as their possible roles in inflammation-induced sensitization processes. In addition, we studied the possible enhancement of antinociception when combined with cyclooxygenase (COX) inhibitors, such as paracetamol (PAR) and its NO-derivative nitroparacetamol (NOP).

The recording of single motor units (SMU) in male Wistar rats showed that MED was a very efficacious antinociceptive agent, reducing the responses to noxious mechanical stimulation in animals with inflammation. In behavioral and electrophysiological experiments, we observed that its antihyperalgesic effect depends on the time course of inflammation, being more intense in the phase of maintenance than in the early or resolution stages. This effect is mainly located supraspinally, because it was more pronounced in animals with an intact spinal cord than in spinalized animals. The administration of subanalgesic doses of NOP induced a significant enhancement of the intensity and duration of the antinociceptive effect of MED. This observation might be useful in the therapy against pain, specially when considering the reduction of the dose required to induce analgesia.

The oral administration of ATRA induces an enhancement of the nociceptive withdrawal reflexes evoked by mechanical and thermal stimulation in behavioral experiments, either in normal animals or in animals with inflammation. Likewise, ATRA induces a sensitization-like effect on spinal cord neuronal responses, similar to that observed by the induction of inflammation, i.e. decreased thresholds for natural and electrical stimulation and enlargement of cutaneous receptive fields. Thus, ATRA

seems to be involved in the mechanisms underlying the generation and/or maintenance of sensitization in the spinal cord. The mechanism of action includes the activation of RAR receptors and the up-regulation of the expression of COX enzymes in dorsal and ventral horn areas of the lumbar spinal cord assessed by Western blot analysis and immunohistochemistry. Since COX enzymes are the substrate of action of COX inhibitors, we studied, using the recording of SMU technique, the analgesic activity of PAR and NOP in the presence and in the absence of ATRA. We observed that the antinociceptive activity of NOP in normal animals, but not PAR, increased in the presence of oral ATRA up to a level similar to that seen in animals with inflammation and without ATRA. This increased analgesic activity might be due to the up-regulation of the expression of COX enzymes induced by ATRA.

Finally we studied the possible antinociceptive interaction of ATRA with MED, fentanyl (FEN) and S-ketoprofen (S-KET). The oral administration of ATRA did not induce a significant enhancement of the antinociceptive effect of any of the compounds studied. However, additional experiments showed an important enhancement of S-KET activity when injected intrathecally, confirming a central, but not peripheral, interaction of ATRA and COX-activity.