The text below is a translation of a Ph.D. thesis abstract from Brazilian Portuguese to US English.

ABSTRACT

Osteoarthritis (OA) is a degenerative and progressive disease characterized by the breakdown of the cartilage that covers the bone ends and the synovial membrane inflammation, causing physical disability, joint swelling, and pain. Although relieving severe pain is the primary goal of OA treatment, the mechanisms involved in the development of pain in OA are little known. Studies have demonstrated the involvement of ATP (adenosine 5'-triphosphate) in the hyperalgesia processes through activating purinergic receptors P2X3, P2X2/3, and P2X7. Therefore, the objectives of this study were: (1) to investigate the involvement of P2X3, P2X2/3, and P2X7 receptors in articular hyperalgesia in a male and female rats, using the rat model of knee joint OA, and if so, whether there are sex differences in the effect induced by P2X3, P2X2/3, and P2X7 receptor antagonists; (2) to test the hypothesis that carrageenan-induced rats' knee joint inflammation increases the expression of P2X3 receptor in chondrocytes of rats' knee joint cartilage; (3) to verify if the mechanism by which the activation of P2X3, P2X2/3, and P2X7 receptors contributes to articular hyperalgesia depends on the prior release of pro-inflammatory cytokines and neutrophil migration; (4) to investigate whether the activation of P2X3, P2X2/3, and P2X7 receptors induces hyperalgesia in the rats' knee joint dependent on the inflammatory mediators release; (5) to test the hypothesis that the activation of P2X3, P2X2/3, and P2X7 receptors contributes to articular hyperalgesia induced by the inflammatory mediators: bradykinin, pro-inflammatory cytokines, PGE2, and dopamine. For objectives 1, 4, and 5, the articular hyperalgesia was quantified using the Rat Knee Joint Incapacitation Test. For objective 2, an immunofluorescence assay was used. For objectives 3 and 4, the Enzyme-linked immunosorbent assay (ELISA) and the measurement of myeloperoxidase (MPO) activity were used. The results demonstrate that the activation of P2X3, P2X2/3, and P2X7 receptors by endogenous ATP is essential for the development of carrageenan-induced articular hyperalgesia in male and estrus female rats, which are more sensitive than male rats to the anti-hyperalgesic and anti-inflammatory effects induced by P2X7 receptor antagonist. During carrageenan-induced joint inflammation, there is an increased expression of P2X3 receptors in the chondrocytes of the rats' knee joint cartilage. The role of P2X3, P2X2/3, and P2X7 receptors in articular hyperalgesia is mediated by indirect sensitization of primary afferent nociceptors, dependent on the prior release of pro-inflammatory cytokines and neutrophil migration. In addition, P2X3, P2X2/3, and P2X7 receptors activation induces articular hyperalgesia, which depends on the release of bradykinin, sympathomimetic amines,

prostaglandins, and pro-inflammatory cytokines. Finally, the articular hyperalgesia induced by the inflammatory mediators bradykinin, PGE2, and dopamine depends on the activation of P2X3 and P2X2/3 receptors. In contrast, the activation of the P2X7 receptor contributes to articular hyperalgesia induced only by bradykinin and dopamine. In conclusion, the results suggest that P2X3, P2X2/3, and P2X7 receptors are interesting pharmacological targets for treating joint inflammatory diseases such as osteoarthritis. Particularly regarding the P2X7 receptor, selective antagonists can be used to reduce pain and inflammation in the knee, especially in women.