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Steroidal and non-steroidal third-generation aromatase inhibitors induce pain-like symptoms via TRPA1

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Use of aromatase inhibitors (AIs), exemestane, letrozole and anastrozole, for breast cancer therapy is associated with severe pain symptoms, the underlying mechanism of which is unknown. The electrophilic nature of AIs suggests that they may target the transient receptor potential ankyrin 1 (TRPA1) channel, a major pathway in pain transmission and neurogenic inflammation. AIs evoke TRPA1-mediated calcium response and current in rodent nociceptors and human cells expressing the recombinant channel. In mice, AIs produce acute nociception, which is exaggerated by pre-exposure to proalgesic stimuli, and, by releasing sensory neuropeptides, neurogenic inflammation in peripheral tissues. AIs also evoke mechanical allodynia and decreased grip strength, which do not undergo desensitization on prolonged AI administration. These effects are markedly attenuated by TRPA1 pharmacological blockade or in TRPA1-deficient mice. TRPA1 is a major mediator of the proinflammatory/proalgesic actions of AIs, thus suggesting TRPA1 antagonists for the treatment of pain symptoms associated with AI use.