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. By using pharmacological or genetic tools, we found that AIs evoke TRPA1-mediated calcium response and current in rodent dorsal root ganglion neurons and in human cells expressing the recombinant or native 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 upon prolonged AIs administration. These effects are markedly attenuated by TRPA1 pharmacological blockade or in TRPA1-deficient mice. The ability of AIs to activate sensory nerve terminals, *via* the TRPA1 channel may be responsible for the inflammatory and painful side effects related to AIs therapy. Present findings suggest that a TRPA1 antagonist could be useful in the treatment of patients with painful states evoked by AIs.

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