Aromatase inhibitor-evoked pain is promoted by the enzyme substrate, androstenedione, via transient receptor potential ankyrin 1 (TRPA1) in mice

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Aromatase inhibitors (AIs) are a mainstay in the treatment of estrogen-sensitive breast cancer in postmenopausal women. AIs block the activity of aromatase cytochrome P450, which, however, rather selectively transforms the androgens, androstenedione and testosterone into the estrogens, responsible for cancer cell replication and growth. Unfortunately, one-third of patients treated with AIs develop muscular and joint pain and inflammation (aromatase inhibitor-associated musculoskeletal symptoms, AIMSS), and also exhibit symptoms of neuropathic or mixed pain. AIMSS and the associated forms of pain represent a major medical problem because they affect the quality of life of the patients, thus limiting treatment adherence, and sometimes leading to therapy discontinuation. Furthermore, AIMSS respond poorly to current analgesic therapies, and the therapeutic needs of the patients remain unmet.

We reported that the transient receptor potential ankyrin 1 (TRPA1), a cation channel highly expressed by a subpopulation of primary sensory neurons of the dorsal root ganglia (DRG), mediates the entire constellation of pain-like behaviors evoked by AIs in mice. However, as aromatase inhibitor concentrations required to engage TRPA1 are higher than those found in patients' plasma, we hypothesized that additional factors might cooperate with the anticancer drugs to promote AIMSS.

Here, we report that the aromatase substrate, androstenedione(ASD), unique among several steroid hormones, targets TRPA1 in peptidergic primary sensory neurons in rodents and in human cells expressing the native or recombinant channel. By in vitro studies, we show that androstenedione selectively activates the recombinant and native human TRPA1 by targeting key electrophilic amino acid residues and excites DRG neurons by TRPA1.

Behavioral test (Von frey hair) was then used to study the mechanical hypersensitivity. We show that intraperitoneal administration of ASD (0.2-2 μg/kg, i.p.) induces a dose dependent mechanical allodynia via the activation of TRPA1.

ASD (2 μg/kg, i.p.) also increases H_2O_2 levels in the sciatic nerve. To better understand the contribution of androstenedione and oxidative stress to the AIMSS-like behaviors, a low dose of ASD (0.2 μg/kg, i.p.) that failed to affect H_2O_2 generation, as well as mechanical allodynia, is used. Systemic ASD (0.2 mg/kg, i.p.) and letrozole (0.1 mg/kg, i.g.) that per se, or in combinations (letrozole/androstenedione) did not affect mechanical allodynia, when given simultaneously caused remarkable mechanical allodynia via the activation of TRPA1.

The present study robustly underscores the role of TRPA1 in ASD-evoked AIMSS-like behaviors. Thus, TRPA1 blockade by both new compounds currently under clinical scrutiny for pain therapy

and old medicines recently identified as TRPA1 antagonists may represent a new frontier to treat or even prevent AIMSS.

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