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NK3R antagonism reduces fear expression in a PTSD-like model of female mice

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The Tachykinin 2 pathway has been shown to modulate fear memory consolidation in healthy animals and humans. Here, we studied the Tac2 pathway antagonist Osanetant administered shortly after immobilization stress on fear memory consolidation in female mice. Osanetant reduced freezing during fear expression, indicating diminished fear memory consolidation. These findings support the potential preventive therapeutic role of Osanetant in a posttraumatic stress disorder-like model.

Fear is a survival mechanism triggered by certain threats that result in instant defensive responses, allowing one to preserve their well-being. Fear memory refers to the association between a neutral and an aversive stimulus (unconditioned stimulus). This results in the neutral stimulus (now termed conditioned stimulus) eliciting a fear response, which, before the association, was only triggered by the unconditioned stimulus. Despite being an adaptative response, fear memory can be altered and can manifest pathological characteristics as often seen in posttraumatic stress disorder (PTSD). Women are twice as likely as men to suffer from PTSD, as seen from their lifetime prevalence (5%–6% in men, 10%–12% in women) (1). Several studies highlight key differences in fear memory processing in males and females both in rodents and humans at anatomical, molecular, and behavioral levels. However, there is still a disparity in the number of studies in males compared to females (5.5:1), emphasizing the need to consider sex as a biological variable in research (2).

The Tachykinin 2 (Tac2) pathway is involved in neuromodulation and neurotransmission in the central nervous system. The Tac2 gene encodes Neurokinin B (NkB), a neuropeptide that binds to the Neurokinin 3 receptor (Nk3R). Previous studies have emphasized the importance of the Tac2 pathway in fear memory modulation (3, 4). Additionally, Tac2 is expressed in key fear-processing areas, including the centromedial amygdala, the bed nucleus of the stria terminalis, and the hippocampus. Blocking the Tac2 pathway could be a potential therapeutic approach for PTSD (3).

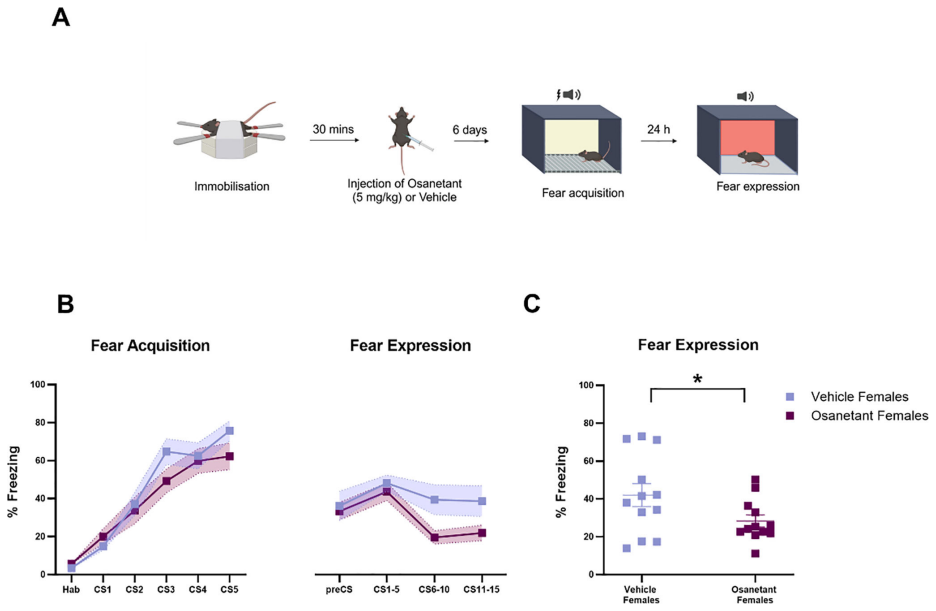

Figure 1. Nk3R antagonism decreases fear memory consolidation. (A) Experimental procedure of fear memory consolidation after stress. Created with Biorender. (B) Fear acquisition and expression in mice administered with Osanetant. (C) Effect in the fear memory consolidation after administration of Osanetant (5 mg/kg, ip) or Vehicle 30 min after stress (IMO) in adult females ($n = 12$ per group) ($p = 0.038$, $\eta^2 = 0.798$). Analyzed by Generalized Linear Model with least significant difference (LSD) correction.

Previous work from our research group has demonstrated that Osanetant, an Nk3R antagonist shows a sex-opposite effect in fear memory consolidation in nonstressed mice, increasing fear expression in females and decreasing it in males (4). Here, we aim to study the effect of Osanetant on fear memory consolidation in female mice subjected to **immobilization stress** (IMO), a PTSD-like model.

Here, Osanetant (5 mg/kg) was administered systemically 30 min after IMO, and 6 days later the mice were subjected to classical fear conditioning (For further details see *supporting online material*). No differences were found in fear acquisition in females administered with Osanetant or vehicle. Interestingly, a treatment effect was seen in female mice ($\chi^2_{(1)} = 4.299$, $p = 0.038$), wherein female mice administered with Osanetant showed lower rates of freezing compared to the Vehicle group during fear expression, indicating decreased fear memory consolidation ($p = 0.038$, $\eta^2 = 0.798$) (Figure 1).

This study highlights the potential therapeutic use of the Nk3R antagonist Osanetant administered immediately after trauma exposure such as car accidents or sexual abuse to prevent pathological alterations of fear processing in women. Among the limitations of this study are the lack of monitoring of the estrous cycle, the exclusion of male mice, and the absence of additional techniques beyond the behavioral protocol. A previous report demonstrated an increase in fear memory consolidation in nonstressed females administered with Osanetant, in apparent contradiction to our current findings (4). We hypothesize that the high intensity of the stressor might be triggering neural changes that are not seen when mice undergo fear acquisition with no previous stress exposure (5). For instance, restraint stress showed to modulate the BDNF, GSK-3β,

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and β-catenin pathway, decreasing the expression of phosphorylated GSK-3β, and β-catenin in the hippocampus of rats (6). However, nonstressed female mice administered with Osanetant after fear acquisition showed an increase in the β-catenin levels (4). This interplay between the levels of β-catenin and potential involvement of other synaptic plasticity factors like mTOR and CREB could be one possible explanation for a decrease in fear memory consolidation in female mice, contrary to nonstressed mice. Further research on the molecular changes of the Tac2 system in the brain under different stress conditions could potentially lead these findings to be translated to the clinic, since Osanetant is a well-tolerated drug in humans (7).

Data Availability

Data will be shared upon reasonable request.

Author Contributions

N.A. and J.F.N. performed the behavioral experiment, analyzed the data, and wrote the manuscript. R.A. conceptualized and oversaw the project, helped writing the manuscript and obtained the funding.

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Author Disclosures

R.A. declares a potential conflict of interest with the patents PCT/US2015/037629 and EP25160662.0. The other authors declare no competing interests.

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