

Ryanodine Receptor-Mediated Calcium Dysregulation as a Therapeutic Target for Treatment of Depression and Anxiety: A Commentary

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Commentary

Major depressive disorder and anxiety disorders together represent one of the largest sources of disability worldwide, and both remain difficult to treat [1,2]. A substantial share of patients fails to respond to first-line antidepressants, and relapse after apparent remission is common [3,4]. Ketamine and esketamine, antagonists of N-Methyl-D-aspartate (NMDA) receptors, have shown that correcting glutamatergic and Ca^{2+} signaling abnormalities can produce rapid symptomatic improvement even in treatment-resistant cases, but their use is constrained by abuse liability, dissociative side effects, and the need for monitored administration [5,6]. There is accordingly considerable interest in identifying other agents that act on the same upstream Ca^{2+} -handling machinery with minimal side effects and toxicity. Dantrolene, a ryanodine receptor (RyR) antagonist and a clinically available drug to treat malignant hyperthermia, has been demonstrated to inhibit NMDA-mediated elevation of cytosolic Ca^{2+} concentration by as much as 78% in cortical neurons [7]. Our recent study makes a notable contribution to this effort by repurposing intranasal dantrolene nanoparticles in Ryanodex formulation for the treatment of depression and anxiety [8].

Summary of Key Findings

Using a well-established LPS-injection model of neuroinflammation-associated mood disturbance, the authors show that four weeks of daily intranasal dantrolene nanoparticles in Ryanodex formulation [9,10] pretreatment substantially blunts the depressive-like (forced swim test, tail suspension test) and anxiety-like (elevated plus maze,

open field test) behaviors that follow a single intraperitoneal LPS challenge. Mechanistically, dantrolene pretreatment suppressed the LPS-induced rise in the pyroptosis-associated cytokines IL-1 β and IL-18 in both serum and brain, attenuated activation of the NLRP3-caspase-1-GSDMD pyroptotic cascade (most clearly for cleaved caspase-1), and preserved the synaptic proteins PSD-95 and synapsin-1, both markers of dendritic spine integrity that are typically eroded by neuroinflammatory insults. Vehicle-treated animals did not share in these benefits, arguing against a nonspecific effect of the nanoparticle carrier itself. An intriguing secondary observation was that behavioral protection was more consistent and robust in female mice than in male mice, a pattern the authors link to the higher clinical prevalence of depression in women and to previously proposed hormonal and stress-axis explanations for that sex disparity.

Why This Matters

The conceptual appeal of this work lies in its intervention in the pathological cascade. Much of the field's therapeutic effort in inflammation-associated depression has focused on cytokines themselves or on downstream neurotransmitter systems. Here, the authors target RyR-mediated Ca^{2+} release from the endoplasmic reticulum (ER), a step upstream of mitochondrial dysfunction, oxidative stress, and inflammasome assembly, as a proposed mechanism. If RyR overactivation is genuinely an early node feeding into pyroptotic cell death, cytokine release, and synapse loss, then a RyR antagonist should in principle produce broader protection than agents aimed at a single downstream mediator. Furthermore, the multi-endpoint improvement reported here (behavior, circulating cytokines,

brain cytokines, pyroptosis markers, and synaptic proteins moving together) is consistent with that logic, even though the causal chain linking these endpoints needs further studies. More studies are needed to investigate the underlying effect and mechanism of dantrolene on inflammatory pyroptosis. Our recent study demonstrating dantrolene's effectiveness to inhibit inflammatory pyroptosis in brains of 5XFAD mice [11], which may provide some assurance that dantrolene may be effective in inhibiting neuronal programmed cell death by pyroptosis.

The choice of intranasal nanoparticle delivery is also pertinent to translatability. Dantrolene is limited by its penetration into the brain [12]. Our earlier pharmacokinetic work, cited in the paper, indicates that intranasal delivery of dantrolene nanoparticles in Ryanodex formulation raises the brain-to-blood concentration ratio relative to oral or subcutaneous routes, and that chronic intranasal dosing up to 10 months in prior Alzheimer's disease models did not produce detectable nasal, hepatic, or muscular toxicity [9,10,13]. Although previous studies have demonstrated an increased brain-to-blood concentration ratio following dantrolene administration, this finding alone does not establish effective CNS target engagement. Nevertheless, intranasal dantrolene nanoparticles may enable lower doses than those required for traditional intravenous, subcutaneous, or oral administration, while still achieving therapeutically relevant CNS concentrations. By increasing CNS delivery while reducing systemic exposure, this approach could potentially lower peripheral blood dantrolene concentrations and minimize dose-related adverse effects, particularly the hepatotoxicity associated with chronic use. Notably, chronic use of dantrolene for up to 10 months did not significantly alter nasal tissue structure in mice [13]. However, because the ratio of nasal surface area to total body size is substantially lower in humans than in mice, the translational efficacy and safety of intranasal dantrolene nanoparticles remain to be established. Further studies in humans are therefore necessary to determine their CNS target engagement, therapeutic efficacy, and potential adverse effects.

The sex-difference finding deserves particular attention from readers in experimental neurology, where preclinical sex-stratified data remain underreported. That the anxiolytic and antidepressant-like effects of dantrolene were most pronounced in females is at minimum a signal that RyR-dependent mechanisms may be differentially weighted between sexes in stress- and inflammation-related psychiatric pathology, and it strengthens the rationale for including both sexes, and reporting them separately, in future mechanistic and dose-ranging studies of this compound class. Although these findings are consistent with the higher prevalence of depressive disorders among female patients, future studies with adequate statistical power are needed to investigate the underlying mechanisms and account for hormonal and estrous cycle status.

Depressive symptoms are highly prevalent across neurodegenerative diseases, affecting up to 50% of patients with Alzheimer's disease [14,15], 35% of stroke patients [16], and 40% of patients with amyotrophic lateral sclerosis (ALS) [17]. Dantrolene, particularly when delivered intranasally via nanoparticle formulations, has demonstrated neuroprotective effects across multiple animal models of these conditions: in models of Alzheimer's disease [10,18–20], cerebral ischemia [21–23], and, in our own recent work, in SOD1G93A transgenic mice, a widely used model of ALS [24]. Given this convergence of evidence, a single agent capable of both protecting against neurodegeneration and ameliorating the depression and anxiety that so commonly accompany these diseases would represent a particularly attractive therapeutic strategy.

Points Warranting Further Scrutiny

A few aspects of the study temper how far its conclusions can presently be extended. First, this is a pretreatment paradigm: dantrolene was administered for four weeks before the inflammatory challenge, which models prevention rather than treatment of an already-established depressive or anxious state. Whether dantrolene nanoparticle treatment began after the onset of inflammation-associated behavioral change would produce comparable reversal is a clinically more relevant question. Second, the LPS single-injection paradigm captures acute neuroinflammatory mood disturbance but does not recapitulate the chronicity of clinical MDD or anxiety disorders. Therefore, validation in chronic stress or chronic low-dose LPS models would strengthen generalizability. Third, the pyroptosis data are uneven: NLRP3 and N-terminal GSDMD changes did not reach statistical significance despite trending in the expected direction, and only cleaved caspase-1 showed a clear effect. Thus, the mechanistic claim that dantrolene acts specifically through inhibition of pyroptosis, as opposed to a more general anti-inflammatory or Ca^{2+} -stabilizing action, remains to be firmly established. Fourth, although dantrolene is extensively studied as an RyR antagonist, it may also have some off-target effects. Dantrolene has been demonstrated to inhibit NMDAR by antagonizing the glycine site [25] on NMDAR and to inhibit Ca^{2+} influx via NMDAR [26]. Thus, the current study has proposed a mechanism but has not confirmed the RyR-mediated Ca^{2+} dysregulation as a causal pathway. The effects of dantrolene on NMDAR warrant further study to determine whether its effects on intracellular Ca^{2+} concentrations result from inhibition of NMDAR, RyR, or both. The authors are appropriately candid about this limitation. Finally, brain tissue was analyzed in bulk rather than by region, which may have obscured effects localized to structures classically implicated in mood regulation, such as the hippocampus, prefrontal cortex, or amygdala, and the absence of direct cytosolic or mitochondrial Ca^{2+} measurements leaves the core mechanism proposed rather than demonstrated.

Future Directions

Several experiments would meaningfully extend this work. Dose-response and treatment-after-onset studies are a priority, given that physiological ER Ca^{2+} release itself is necessary for normal neuronal signaling and excessive RyR blockade could have its own costs. Region-specific and cell-type-specific analyses (neuronal versus microglial versus astrocytic) would help clarify where dantrolene's protective effects are exerted. Direct measurement of reactive oxygen species and of cytosolic/mitochondrial Ca^{2+} flux would close the mechanistic gap between RyR inhibition and the downstream inflammatory and synaptic readouts reported here. Given the sex-difference finding, mechanistic studies stratified by sex and, eventually, by estrous/hormonal status would be valuable. Finally, because the model here is inflammation-induced rather than genetic- or chronic-stress-induced, cross-model replication would help establish whether dantrolene's benefits generalize across the heterogeneous biological routes to depressive and anxious phenotypes.

Conclusion

This study provides promising preclinical proof of concept for further investigation of RyR/ Ca^{2+} signaling in inflammation-associated behavioral dysfunction. Confirmatory studies addressing treatment rather than prevention, timing, chronic models, regional and mechanistic specificity, and dose optimization will be important for determining whether intranasal dantrolene nanoparticles can advance toward clinical evaluation as a novel therapeutic approach for depression and anxiety with a potentially improved safety profile. Given previous evidence supporting the role of RyR/ Ca^{2+} signaling and dantrolene in neurodegenerative disorders, including Alzheimer's disease and amyotrophic lateral sclerosis, these findings may also have broader implications for future investigation of intranasal dantrolene as a therapeutic strategy across neurological and neuropsychiatric conditions.

Conflict of Interest

Dr. Huafeng Wei is listed as an inventor of patents and an ongoing application entitled "Intranasal Administration of Dantrolene for Treatment of Alzheimer's Disease" in multiple countries by The Trustees of the University of Pennsylvania. Dr. Huafeng Wei is listed as the inventor of the USA and an ongoing international patent application repurposing intranasal dantrolene nanoparticles with or without lithium to treat major depression disorder and amyotrophic lateral sclerosis (PCT/US2026/016152).

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References

1. Wang Z, Dou Y, Yang X, Guo X, Ma X, Zhou B, et al. Global, regional, and national burden of mental disorders among adolescents and young adults, 1990–2021: a systematic analysis for the Global Burden of Disease Study 2021. *Transl Psychiatry*. 2025 Oct 10;15(1):397.
2. Ferrari AJ, Charlson FJ, Norman RE, Patten SB, Freedman G, Murray CJ, et al, Whiteford HA. Burden of depressive disorders by country, sex, age, and year: findings from the global burden of disease study 2010. *PLoS Med*. 2013 Nov;10(11):e1001547.
3. Rush AJ, Trivedi MH, Wisniewski SR, Nierenberg AA, Stewart JW, Warden D, et al. Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR*D report. *Am J Psychiatry*. 2006 Nov;163(11):1905–17.
4. Otte C, Gold SM, Penninx BW, Pariante CM, Etkin A, Fava M, et al. Major depressive disorder. *Nat Rev Dis Primers*. 2016 Sep 15;2:16065.
5. Krystal JH, Abdallah CG, Sanacora G, Charney DS, Duman RS. Ketamine: A Paradigm Shift for Depression Research and Treatment. *Neuron*. 2019 Mar 6;101(5):774–8.
6. McIntyre RS, Rosenblat JD, Nemeroff CB, Sanacora G, Murrough JW, Berk M, et al. Synthesizing the Evidence for Ketamine and Esketamine in Treatment-Resistant Depression: An International Expert Opinion on the Available Evidence and Implementation. *Am J Psychiatry*. 2021 May 1;178(5):383–99.
7. Frandsen A, Schousboe A. Mobilization of dantrolene-sensitive intracellular calcium pools is involved in the cytotoxicity induced by quisqualate and N-methyl-D-aspartate but not by 2-amino-3-(3-hydroxy-5-methylisoxazol-4-yl)propionate and kainate in cultured cerebral cortical neurons. *Proc Natl Acad Sci U S A*. 1992 Apr 1;89(7):2590–4.
8. Liu J, Lu Y, Bhuiyan P, Gruttner J, St Louis L, Yi Y, et al. Intranasal dantrolene nanoparticles inhibit lipopolysaccharide-induced depression and anxiety behavior in mice. *Transl Psychiatry*. 2026 Feb 3;16(1):104.
9. Wang J, Shi Y, Yu S, Wang Y, Meng Q, Liang G, et al. Intranasal administration of dantrolene increased brain concentration and duration. *PLoS One*. 2020 Mar 11;15(3):e0229156.
10. Shi Y, Zhang L, Gao X, Zhang J, Ben Abou M, Liang G, et al. Intranasal Dantrolene as a Disease-Modifying Drug in Alzheimer 5XFAD Mice. *J Alzheimers Dis*. 2020;76(4):1375–89.
11. Bhuiyan P, Zhang W, Chae R, Kim K, St Louis L, Wang Y, et al. Intranasal dantrolene nanoparticles inhibit inflammatory pyroptosis in Alzheimer's disease model mouse brain. *Br J Anaesth*. 2025 May;134(5):1574–77.
12. Wuis EW, Rijntjes NV, Van der Kleijn E. Whole-body autoradiography of ^{14}C -dantrolene in the marmoset monkey. *Pharmacol Toxicol*. 1989 Jan;64(1):156–8.

13. Jiang B, Shi Y, Abou MB, Xu L, Liang G, Wei H. Effects of chronic intranasal dantrolene on nasal mucosa morphology in mice. *Eur Rev Med Pharmacol Sci*. 2022 Jan;26(1):198–203.
14. Crump C, Sieh W, Vickrey BG, Edwards AC, Sundquist J, Sundquist K. Risk of depression in persons with Alzheimer's disease: A national cohort study. *Alzheimers Dement (Amst)*. 2024 Apr 14;16(2):e12584.
15. Zubenko GS, Zubenko WN, McPherson S, Spoor E, Marin DB, Farlow MR, et al. A collaborative study of the emergence and clinical features of the major depressive syndrome of Alzheimer's disease. *Am J Psychiatry*. 2003 May;160(5):857–66.
16. Naghedi A, Delgado-Mederos R, Vives-Bauza C. Stroke Survivors Have Almost Three Times Higher Risk of Depression: A Systematic Review and Meta-Analysis. *J Clin Med*. 2025 Nov 27;14(23):8410.
17. Jellinger KA. Understanding depression with amyotrophic lateral sclerosis: a short assessment of facts and perceptions. *J Neural Transm (Vienna)*. 2024 Feb;131(2):107–15.
18. Peng J, Liang G, Inan S, Wu Z, Joseph DJ, Meng Q, et al. Dantrolene ameliorates cognitive decline and neuropathology in Alzheimer triple transgenic mice. *Neurosci Lett*. 2012 May 16;516(2):274–9.
19. Oulès B, Del Prete D, Greco B, Zhang X, Lauritzen I, Sevalle J, et al. Ryanodine receptor blockade reduces amyloid- β load and memory impairments in Tg2576 mouse model of Alzheimer disease. *J Neurosci*. 2012 Aug 22;32(34):11820–34.
20. Chakroborty S, Briggs C, Miller MB, Goussakov I, Schneider C, Kim J, et al. Stabilizing ER Ca²⁺ channel function as an early preventative strategy for Alzheimer's disease. *PLoS One*. 2012;7(12):e52056.
21. Wei H, Perry DC. Dantrolene is cytoprotective in two models of neuronal cell death. *J Neurochem*. 1996 Dec;67(6):2390–8.
22. Li F, Hayashi T, Jin G, Deguchi K, Nagotani S, Nagano I, et al. The protective effect of dantrolene on ischemic neuronal cell death is associated with reduced expression of endoplasmic reticulum stress markers. *Brain Res*. 2005 Jun 28;1048(1-2):59–68.
23. Nakayama R, Yano T, Ushijima K, Abe E, Terasaki H. Effects of dantrolene on extracellular glutamate concentration and neuronal death in the rat hippocampal CA1 region subjected to transient ischemia. *Anesthesiology*. 2002 Mar;96(3):705–10.
24. Bhuiyan P, Yi Y, Wei B, Yan A, Dong L, Wei H. Intranasal Dantrolene Nanoparticles for Treatment of Amyotrophic Lateral Sclerosis as a Disease-Modifying Drug. *bioRxiv [Preprint]*. 2025 May 27:2025.05.21.655232.
25. Salinska E, Sobczuk A, Lazarewicz JW. Dantrolene antagonizes the glycineB site of the NMDA receptor. *Neurosci Lett*. 2008 Feb 20;432(2):137–40.
26. Makarewicz D, Ziemińska E, Łazarewicz JW. Dantrolene inhibits NMDA-induced ⁴⁵Ca uptake in cultured cerebellar granule neurons. *Neurochem Int*. 2003 Sep-Oct;43(4-5):273–8.