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N-palmitoyl-D-glucosamine reduces pain behaviours and inflammation in an experimental dysbiosis condition

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Federica Ricciardi [1], Antimo Fusco [1], Iolanda Manzo [1], Andrea Maria Morace [1], Michela Perrone [1], Livio Luongo [2], Francesca Guida [3], Sabatino Maione [4]

1. Department of Experimental Medicine, Division of Pharmacology, University of Campania “L. Vanvitelli”, Napoli, ITA 2. Department of Experimental Medicine, Division of Pharmacology, University of Campania "Luigi Vanvitelli", Napoli, ITA 3. Department of Experimental Medicine, Division of Pharmacology, University of Campania, Napoli, ITA 4. Division of Pharmacology Department of Experimental Medicine, University of Campania, Napoli, ITA

Corresponding author: Federica Ricciardi, federica.ricciardi1@unicampania.it

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Abstract

Background
Increasing evidence shows that intestinal microbiota plays a significant role in pain modulation through its bidirectional communication with the enteric and central nervous systems (ENS and CNS) (Morreale et al., 2022). Microbiota and its metabolites influence emotional behaviors and pain, suggesting that restoring gut microbiota could be a new therapeutic strategy for treating neurosensory and psychiatric disorders associated with inflammation.

Research highlights the role of immune pathways in pain, by identifying toll-like receptor 4 (TLR4) as crucial in the inflammatory response. Its activation is associated with the release of cytokines and inflammatory mediators, contributing to the gastrointestinal inflammation (M. Cuesta et al., 2021). N-palmitoyl-D-glucosamine (PGA), a natural compound produced by bacteria such as Rhizobium leguminosarum, has demonstrated anti-inflammatory properties in animal models. Computational molecular docking also confirmed PGA's binding to the MD2 domain of TLR4 (Iannotta et al., 2021;).

This study used a model of dysbiosis in healthy mice exposed to a broad-spectrum antibiotics (Ab) cocktail, leading to imbalanced intestinal microbiota, to investigate PGA effects on gut inflammation and related neurosensory alterations.

Methods
C57BL/6J male mice (3-4 weeks) were treated with Ampicillin, Streptomycin, and Clindamycin (1 mg/kg) for 14 days. Control groups received only water. Mice were treated with PGA (10 mg/kg) (Epitech Group SpA) or vehicle (pluronic acid) by oral gavage from day 0 to day 14. Behavioral tests (colon-rectal distension, tail suspension, Y-maze and borrowing tests) and electrophysiological analysis were conducted, along with biomolecular and microbiota analysis

Results
The perturbation of the gut microbiota was associated with an overall inflammatory condition, as suggested by the increase of fecal calprotectin and lipocalin levels in Ab-treated animals. Gut inflammation was associated with a marked colon-distension pain-related behavior along with sickness behaviors, reported as an increased immobility time and reduced burrowing behavior. Additionally, an Ab-induced overexcitation of nociceptive neurons (L4-S1) was detected in terms of firing rate, frequency, and duration of excitation. Repeated administration of PGA ameliorated gut inflammation and visceral pain behavior,and improved all sickness-related behaviors.

Conclusions
Our findings emphasize the intestinal microbiota's role in neurosensory and affective disorders. PGA, by directly binding to TLR4, shows therapeutic potential in these disorders and reduces inflammation linked to dysbiosis. These results highlight the beneficial effects of PGA in neurosensory and affective disorders associated with dysbiosis and suggest further exploration of TLR4 modulation in gut-microbiota interaction.