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The relevance of the 5HT2A–mGlu2 heterodimer in explaining the clinical ambivalence of psilocybin

La relevancia del heterodímero 5HT2A-mGlu2 para explicar la ambivalencia clínica de la psilocibina

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Dear editors,

Psilocybin is an alkaloid found in mushrooms of the *Psilocybe* genus and other species, although it can also be synthesized in the laboratory (1). It is currently under investigation as a therapeutic agent for the treatment of various neuropsychiatric disorders, including depression and anxiety (2).

Due to this renewed interest in its use in both therapeutic and contemporary "spiritual" contexts, psilocybin has given rise to a growing body of research as well as concerns associated with its use, particularly because of some reports of adverse effects (3). This duality reinforces the need to deepen research efforts to clarify its mechanisms of action.

In this context, the main mechanism of action proposed for psilocybin, strongly related to its therapeutic effects, is its agonism at serotonin 5-HT2A receptors located on glutamatergic neurons, especially those in layer V of the cerebral cortex, which promotes neuroplasticity and restores cognitive functions impaired by mental illnesses (4). However, this mechanism alone is insufficient to explain the intersubject variability of reported effects.

Furthermore, the existence of dynamic signaling heteromeric complexes between mGlu2 and 5-HT2A receptors has been described. These complexes are modulated by the activation state of both receptors, with agonism of the mGlu2 receptor inducing or modulating the activity associated with 5-HT2A, thereby promoting the psychoplastogenic properties attributed to psilocybin.

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The function of this heteromeric complex provides an explanatory framework not only for understanding psilocybin's mechanisms of action but also for interpreting the heterogeneity of its effects across individuals. In this regard, variability in its conformation, whether hereditary or congenital, as occurs in certain pathologies (5), could alter associated signaling and create a biological vulnerability to adverse effects.

Recent human studies have documented remarkable heterogeneity in both hemodynamic and subjective responses to psilocybin, even under controlled administration conditions (6). This interindividual variability can be understood considering the dynamics of the mGlu2–5-HT2A heteromer, whose functional ratio and conformational state influence the direction and magnitude of intracellular signaling. Therefore, genetic, epigenetic, or baseline expression differences in these receptors could modulate the balance between excitatory and regulatory pathways, explaining why the same dose of psilocybin triggers divergent effects among subjects. Integrating this mechanistic framework with recent clinical findings opens the door to studies that combine neuroimaging, genetics, and pharmacology, paving the way toward response biomarkers and truly personalized psychopharmacology.

In summary, the 5-HT$_2$A/mGlu2 heteromer should be recognized as a pivotal determinant of psilocybin's pharmacological profile. A rigorous program of basic research is essential to elucidate its function, paving the way for personalized therapeutic strategies and optimized clinical trial designs. Such an approach aligns with the translational mission of neuropsychopharmacology, ensuring that mechanistic insights are directly harnessed to improve patient outcomes. By embracing this receptor-level complexity, the field can move toward a more precise and predictive understanding of psychedelic therapeutics.

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GEC: substantial contribution to the conception of the work and drafting.
JCG, CRR: drafting of the manuscript.
FC: final approval for publication.

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