



OPEN ACCESS

EDITED BY

Alfredo Bellon,
Penn State Milton S. Hershey Medical Center,
United States

REVIEWED BY

Patricio Ernesto Iturriaga-Vasquez,
University of La Frontera, Chile

*CORRESPONDENCE

Francisco Jiménez-Trejo

✉ trejofj@gmail.com

Gustavo Canul-Medina

✉ gustavo.canul.medina@gmail.com

RECEIVED 18 June 2024

ACCEPTED 03 October 2024

PUBLISHED 17 October 2024

CITATION

Jiménez-Trejo F, Jiménez-García KL and
Canul-Medina G (2024) Serotonin and
schizophrenia: what influences what?
Front. Psychiatry 15:1451248.
doi: 10.3389/fpsy.2024.1451248

COPYRIGHT

© 2024 Jiménez-Trejo, Jiménez-García and
Canul-Medina. This is an open-access article
distributed under the terms of the [Creative
Commons Attribution License \(CC BY\)](#). The
use, distribution or reproduction in other
forums is permitted, provided the original
author(s) and the copyright owner(s) are
credited and that the original publication in
this journal is cited, in accordance with
accepted academic practice. No use,
distribution or reproduction is permitted
which does not comply with these terms.

Serotonin and schizophrenia: what influences what?

Francisco Jiménez-Trejo^{1*}, Katia Lorena Jiménez-García²
and Gustavo Canul-Medina^{3*}

¹Cellular and Tissue Morphology Laboratory, National Institute of Pediatrics, Mexico City, Mexico,

²Faculty of Medicine, Universidad Nacional Autónoma de México, Mexico City, Mexico, ³School of
Medicine, Educational Center Rodríguez Tamayo, Merida, Mexico

KEYWORDS

serotonin, schizophrenia, neurotransmitters, illness, serotoninomics

Introduction

Schizophrenia is a chronic and complicated psychiatric and psychological illness. It is characterized by a set of symptoms that include hallucinations, delusions, speech or behavioral disorders, emotional blunting, anhedonia, alogia, apathy, and other defective cognitive abilities. Schizophrenia is a devastating developmental disorder that arises from the interaction between genetic and environmental factors (1). Several lines of evidence suggest that the serotonergic system plays a critical role in the pathogenesis of schizophrenia in at least a subpopulation of patients. According to the neuropathological changes, this heterogeneous condition has been divided into three main domains: positive symptoms, negative symptoms, and cognitive dysfunction. Additionally, some researchers have conceptualized schizophrenia as a disease of functional “dysconnectivity” (2–4) or “synapse disorder” (5, 6), affecting the serotonin quantum release machinery within the synapse during its synthesis, its interaction with its receptors, or its correlation with other neurotransmitters (i.e. dopamine, glutamate, GABA) (7, 8). Acute relapses of this disease are characterized by the exacerbation of positive psychotic symptoms, while chronic disabilities occur due to cognitive causes and negative symptoms (apathy and social withdrawal) (9). The disease profoundly affects not only the individuals who suffer from it but also their families and caregivers, typically manifesting during late adolescence or early adulthood (1, 9).

Because the condition is so heterogeneous, the presence of symptoms from these domains in the disease makes its diagnosis and treatment difficult. The development of some mental diseases, including schizophrenia, are marked by subtle molecular, heritable, and epigenetic changes, which initiate a cascade of events within individual cells before overt signs and symptoms manifest themselves. These events include effective quantum release; appropriate signaling by receptors and activation by second messengers; the functionality of transporters; the ability to take up, store, and release serotonin; the presence of isoforms; the activity of tryptophan hydroxylase-2 (TPH2; lack of activity); the availability of the amino acid L-

tryptophan (L-Trp); deviation towards other pathways of its metabolism how to as the kynurenine-like pathway; mutations; and other dysfunctions. Therefore, individuals with schizophrenic parents or siblings will have a higher risk of developing the disease due to this hereditary component (between 8% and 12% (10). The most common theory regarding the neurobiology of schizophrenia is a chemical imbalance in the brain, marked by deregulation of the mesolimbic pathway as a result of dopaminergic hyperactivity and, in some cases, alterations in the serotonergic system in specific nuclei of the brain (prefrontal cortex, temporal cortex, thalamus, hypothalamus, and basal ganglia) or in the interaction between dopamine and serotonin (9).

Serotonin is a molecule with numerous functions within the central nervous system (CNS), which is why it plays an essential role in the delicate balance of neuronal function. Alterations in serotonin concentration can contribute to the onset of schizophrenia, and conversely, schizophrenia can gradually affect the serotonergic systems of the brain (11). As the initial molecular and genetic changes progress, often silently and insidiously, these molecular perturbations extend to higher organizational levels: tissues, organs, and systems. In this way, all of these changes will culminate in dysregulations that will contribute to the characteristic symptoms of schizophrenia (i.e. altered perception) (12). A key limitation in the study of schizophrenia is that it is difficult to conclusively determine causation, given the interactive influences exerted by the different molecular and physiological mechanisms involved (9, 11, 12). Therefore, the understanding of these early molecular events is essential for unravelling schizophrenia's etiology, including neurotransmitter dysregulation, neuroinflammation, the hypothalamic–pituitary–adrenal (HPA) axis, the gut–brain axis (GBA), oxidative stress, and mitochondrial dysfunction and thus for developing interventions that could slow down or modulate these processes before symptomatic expression. In recent years, the gut microbiota (GM) has emerged as another important factor in the development of neurological–psychiatric disorders (including schizophrenia), with changes in the composition and quality of individual microbial communities potentially having serious health consequences. This cerebral–gut axis is a two–way communication pathway, in which brain–gut communication occurs through the autonomic nervous system (ANS), mainly the vagus nerve. Research has revealed that approximately 90% of the impulses within the cerebral–intestinal axis are transmitted centripetally —from the intestines to the brain—and only 10% centrally. In this respect, certain intestinal bacteria, such as *Escherichia* spp., *Candida* spp., and *Enterococcus* spp., produce various substances, including serotonin, involved not only in communication within the intestinal microflora but also in systemic and peripheral effects that influence brain function (13).

The reality is that there is a close mutual relationship between serotonin and schizophrenia, and this bidirectionally influences the way in which serotonin manifests itself in this mental illness. But which one comes first: changes in the serotonergic system or schizophrenia? This is an important question to which we seek to provide an answer in this occasion.

Abbreviations: Tryptophan hydroxylase–2, TPH2, L–tryptophan, L–Trp, central nervous system, SNC Serotonin, 5–hydroxytryptamine, 5–HT.

Hierarchy of action versus manifested symptoms

Since its discovery as a molecule by Page et al. in 1948 (14), serotonin (5–hydroxytryptamine, 5–HT, $C_{10}H_{12}N_2O$) has led to great expectations and interest due to the implications it may have for various pathologies, including those related to mental health such as schizophrenia. This disease affects millions of people around the world, making it a main challenge for the community of doctors and scientists who seek to reduce its effects and improve the quality of life of patients. Generally, the disease begins without presenting symptoms in an absolute and pathognomonic manner, unless the disease has a genetic, immune–related, or acutely toxic origin. The body can warn of the disease before the patient perceives any specific signs and symptoms, or it can be recognized through the information provided by the patient's family, so that a diagnosis can be established and specific treatments can be initiated (5, 6).

Like most psychotic diseases, schizophrenia is considered to be caused by an imbalance in neurotransmitters (e.g. dopamine [DA], glutamate, GABA, and serotonin). The simple model of abnormally high DA transmission could not explain the pathophysiology of schizophrenia or the therapeutic actions of antipsychotic medications. Nonetheless, this model has persistently served as the primary explanation for schizophrenia (1). Due to the complexity of its neuropathology, schizophrenia is a complicated disorder. The lack of understanding of its pathophysiology and its different forms and modes of presentation in patients often leads to it being unmanageable as a disease within clinical settings (15).

The global prevalence of schizophrenia is around 1%–1.5%. Between 1990 and 2019, the number of people with schizophrenia increased from 14.2 to 23.6 million (16, 17). Its etiological origin is heterogeneous, and the interaction between genetic (heritability), social (isolation, discrimination), psychological (school bullying, aggressive abuse), and environmental (exposure to metal toxicity) factors complicates etiological and diagnostic counts. However, when any of these interactions occur, it is reflected in many patients, even generating associations with other psychiatric conditions such as depression. Therefore, this comorbidity suggests a potential common pathophysiology and/or common genetic predictors of these mental disorders. Mesolimbic dopamine release in patients experiencing hallucinations or psychotic symptoms is known to cause increased activation of the thalamus, hippocampus, and striatum in the CNS. The hyperactivity of the hippocampus appears to be driven by a loss of parvalbumin–containing gamma–aminobutyric acidergic (GABAergic) interneurons, a phenomenon observed in postmortem analyses of schizophrenia brains.

The molecular mechanisms linking schizophrenia, depression, and other psychiatric diseases are polygenic. Currently, genes candidates under study are *GRIN1*, *GPM6A*, *SEPTIN4*, *TPH1*, *TPH2*, *CACNA1C*, *CACNB2*, *BCL9*, and *C4A* (18). For this last gene, Sekar et al. (2016) postulated that excessive activity of *C4A* during the development of schizophrenia might explain the reduction in the number of synapses in the brains of affected individuals. This gene is associated with the major histocompatibility complex (MHC)

locus, which represents the strongest genetic association of schizophrenia at the population level (19). Other genes are probably involved in schizophrenia, and the complexity of responses to 5-HT may involve other factors, so further studies should be performed for a genetic diagnosis.

More recently, Kossatz et al. (2024) contributed to unravelling the role of 5-HT_{2A}-mediated pathways in schizophrenia-like behavioral responses by applying a multidisciplinary approach, integrating computational modelling, *in vitro* and *in vivo* experiments, and postmortem human brain studies. Since this receptor is a prominent target for the treatment of schizophrenia, they demonstrated that memory deficits are regulated via G α q protein activation, whereas psychosis-related behavior is modulated through G α i1 stimulation (20).

Additionally, recent advances in animal models seek more successful therapeutic approaches within clinical settings related to pathophysiology, such as dopamine, glutamate, GABA, and serotonin. These animal models are based on the release of neurotransmitters, pharmacological interactions, processes during neurodevelopment, and genetics. In schizophrenia, the presence of gene polymorphism has also been reported (e.g., dysbindin, *DICS1*, and *NRG1*). Several hypotheses have been based on dopamine, glutamate, and serotonin, which have served as successful models within schizophrenia studies. Pharmacological therapies have even been designed based on these models, and many of them are still used today (21).

New targets, such as the orexin system, the muscarinic and nicotinic receptors, and the cannabinoid receptors, have been addressed with the aim of alleviating negative and cognitive symptoms. Additionally, non-pharmacological models have been developed, such as the post-weaning social isolation model (maternal deprivation) and the isolation parenting model, with the aims of imitating the symptoms of schizophrenia and creating and testing new approaches to drug therapy, constituting a great advance in treating psychiatric disorders. Different behavioral tests have been evaluated in these specific models. However, while animal models are inherently limited and can only approximate the pathological state observed in humans, if they are based on clinical observations, they are essential for providing insights into the mechanisms of action of novel drug candidates (22). Thus, better translational models and behavioral tests for psychological disorders, such as schizophrenia and related psychiatric conditions, should be more abundant and available (15).

Furthermore, it is important to promote the practical concept of serotoninomics to contribute to the search for precise answers in basic, clinical, and translational research, as well as in clinical pharmacology, particularly concerning mental illnesses such as schizophrenia and/or depression. Our group proposed this concept seeking to encompass all studies focused specifically under the topic of serotonin and its associated system. This includes experimental techniques and laboratory tools that have been used since its discovery until today (23, 24). Adopting this approach can help us in elucidating causal links within a health state, such as alterations of the serotonergic system itself, and the alterations that it produces

within the organs or tissues in which it participates, as well as the wide range of biological systems in which it is present.

Therefore, assessing the scope and limits of our opinion means analyzing, for example, whether the psychotic alterations of schizophrenia in some types of patients, given their characteristics shown, are triggered by alterations in the serotonin system and constitute an ultimate explanation. Thus, secondary consequences will almost always follow psychiatric manifestations, which in this case correspond to patients who attend mental health clinical consultations.

On the other hand, confinement, social distancing, and isolation due to the SARS-CoV-2 (COVID-19) pandemic increased psychological stress and affected people's mental health (25, 26). Realizing that SARS-CoV-2 or other opportunistic microorganisms (e.g. bacteria, viruses, prions, or fungi) can enhance mental health problems in humans is important for combating their effects, which increase as mental conditions are altered (26, 27).

Conclusion

As proposed by Shnyder et al. (18), the planning and performance of associative genetic studies in psychiatric diseases, such as schizophrenia, and the determination of the complete genome of comorbid diseases will be important for the development of gene-based therapies, as well as for clinical predictors based on therapeutic strategies within personalized medicine. These steps must be carried out despite the current problems of predictive and personalized psychiatry in the diagnosis and treatment of comorbid diseases, which are still far from being resolved more than 76 years after the discovery of serotonin. Diagnoses and clinical approaches must be urgently improved to define what type of psychiatric condition the patient presents in order to quickly determine the best pharmacological therapy to reduce their symptoms and abnormal behaviors. Understanding these early molecular events is essential for unravelling the etiology of schizophrenia and for developing interventions that can slow down or modulate these processes before symptomatic expression. Furthermore, systematic reviews (qualitative or quantitative reviews and meta-analysis) and/or bibliometrics may help guide the pharmacological approach, therapeutic decisions, and the continuity of treatment, including the facilitating role of artificial intelligence in human medicine.

Author contributions

FJ-T: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Resources, Supervision, Validation, Writing – original draft, Writing – review & editing. KJ-G: Data curation, Formal analysis, Investigation, Project administration, Resources, Supervision, Writing – original draft,

Writing – review & editing. GC–M: Data curation, Funding acquisition, Investigation, Supervision, Validation, Writing – original draft, Writing – review & editing.

Funding

The author(s) declare that no financial support was received for the research, authorship, and/or publication of this article.

Acknowledgments

We thank Dr. Mercedes Macías Parra and Dr. Sara Elva Espinosa Padilla for her support and vision to continue with this idea. We apologize to all authors whose papers are not cited because of the limitations in the number of references.

References

- Grace AA, Uliana DL. Insights into the mechanism of action of antipsychotic drugs derived from animal models: standard of care versus novel targets. *Int J Mol Sci.* (2023) 24:12374. doi: 10.3390/ijms241512374
- Weinberger DR, Berman KF, Suddath R, Fuller Torrey E. Evidence of dysfunction of a prefrontal–limbic network in schizophrenia: A magnetic resonance imaging and regional cerebral blood flow study of discordant monozygotic twins. *Am J Psychiatry.* (1992) 149:890–7. doi: 10.1176/ajp.149.7.890
- Friston KJ, Frith CD. Schizophrenia: a disconnection syndrome? *Clin Neurosci (New York N.Y.).* (1995) 3:89–97.
- McGlashan TH, Hoffman RE. Schizophrenia as a disorder of developmentally reduced synaptic connectivity. *Arch Gen Psychiatry.* (2000) 57:637–48. doi: 10.1001/archpsyc.57.7.637
- Mirnic K, Middleton FA, Stanwood GD, Lewis DA, Levitt P. Disease-specific changes in regulator of G-protein signaling 4 (RGS4) expression in schizophrenia. *Mol Psychiatry.* (2001) 6:293–301. doi: 10.1038/sj.mp.4000866
- Frankle WG, Lerma J, Laruelle M. The synaptic hypothesis of Schizophrenia. *Neuron.* (2003) 39:205–16. doi: 10.1016/S0896-6273(03)00423-9
- Harrison PJ, Eastwood SL. Neuropathological studies of synaptic connectivity in the hippocampal formation in schizophrenia. *Hippocampus.* (2001) 11:508–19. doi: 10.1002/hipo.1067
- Honer WG, Young CE. Presynaptic proteins and schizophrenia. *Int Rev Neurobiol.* (2004) 59:175–99. doi: 10.1016/S0074-7742(04)59007-4
- Rawani NS, Chan AW, Dursun SM, Baker GB. The underlying neurobiological mechanisms of psychosis: focus on neurotransmission dysregulation, neuroinflammation, oxidative stress, and mitochondrial dysfunction. *Antioxid (Basel).* (2024) 13:709. doi: 10.3390/antiox13060709
- Zorrilla LTE, Jeste DV. Schizophrenia. In: *Encyclopedia of the Human Brain.* San Diego (California): Academic Press (2002). p. 251–62. doi: 10.1016/B0-12-227210-2/00306-X
- Abi-Dargham A. Alterations of serotonin transmission in schizophrenia. *Int Rev Neurobiol.* (2007) 78:133–64. doi: 10.1016/S0074-7742(06)78005-9
- Manassa H, Baryiah R, Azhar Y, Chapman J. *Schizophrenia.* Treasure Island, Florida: StatPearls (2024).
- Góralczyk–Bińkowska A, Szmajda–Krygier D, Kozłowska E. The microbiota–gut–brain axis in psychiatric disorders. *Int J Mol Sci.* (2022) 23:11245. doi: 10.3390/ijms231911245
- Rapport MM, Green AA, Page IH. Serum vasoconstrictor, serotonin, isolation and characterization. *J Biol Chem.* (1948) 176:1243–51. doi: 10.1016/S0021-9258(18)57137-4
- Malik JA, Yaseen Z, Thotapalli L, Ahmed S, Shaikh MF, Anwar S. Understanding translational research in schizophrenia: A novel insight into animal models. *Mol Biol Rep.* (2023) 50:3767–85. doi: 10.1007/s11033-023-08241-7

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

- Bai W, Liu ZH, Jiang YY, Zhang QE, Rao WW, Cheung T, et al. Worldwide prevalence of suicidal ideation and suicide plan among people with schizophrenia: a meta-analysis and systematic review of epidemiological surveys. *Transl Psychiatry.* (2021) 11:552. doi: 10.1038/s41398-021-01671-6
- Solmi M, Seitidis G, Mavridis D, Correll CU, Dragioti E, Guimond S, et al. Incidence, prevalence, and global burden of schizophrenia – data, with critical appraisal, from the Global Burden of Disease (GBD) 2019. *Mol Psychiatry.* (2023) 28:5319–27. doi: 10.1038/s41380-023-02138-4
- Shnayder NA, Novitsky MA, Neznanov NG, Limankin OV, Asadullin AR, Petrov AV, et al. Genetic predisposition to schizophrenia and depressive disorder comorbidity. *Genes.* (2022) 13:457. doi: 10.3390/genes13030457
- Sekar A, Bialas AR, De Rivera H, Davis A, Hammond TR, Kamitaki N, et al. Schizophrenia risk from complex variation of complement component 4. *Nature.* (2016) 530:177–83. doi: 10.1038/nature16549
- Kossatz E, Diez-Alarcia R, Gaitonde SA, Ramon-Duaso C, Stepniowski TM, Aranda-García D, et al. G protein-specific mechanisms in the serotonin 5-HT_{2A} receptor regulate psychosis-related effects and memory deficits. *Nat Commun.* (2024) 15:4307. doi: 10.1038/s41467-024-48196-2
- Yang AC, Tsai SJ. New targets for schizophrenia treatment beyond the dopamine hypothesis. *Int J Mol Sci.* (2017) 18:1689. doi: 10.3390/ijms18081689
- Uliana DL, Gomes FV, Grace AA. Update on current animal models for schizophrenia: Are they still useful? *Curr Opin Psychiatry.* (2023) 36:172–8. doi: 10.1097/YCO.0000000000000854
- Jiménez-Trejo F, Tapia-Rodríguez M. Exploring the frontiers of serotoninomics in male reproduction: the future ahead. *Single Cell Biol.* (2015) 04:3. doi: 10.4172/2168-9431.1000115
- Jiménez-Trejo F, Tapia-Rodríguez M, Arriaga-Canon C, Herrera LA, Contreras-Espinoza L, Jiménez-García KL. Expanding the concept of serotoninomics: perspectives for serotonin studies in the 20's of the 21st century. *Front Neurosci.* (2023) 17:1200370. doi: 10.3389/fnins.2023.1200370
- Szcześniak D, Gładka A, Misiak B, Cyran A, Rymaszewska J. The SARS-CoV-2 and mental health: From biological mechanisms to social consequences. *Prog Neuro-Psychopharmacol Biol Psychiatry.* (2021) 104:110046. doi: 10.1016/j.pnpbp.2020.110046
- Pourfridoni M, Askarpour H. COVID-19 and the increase in schizophrenia incidence in the future: A hypothesis and a serious warning. *Health Sci Rep.* (2023) 6:e978. doi: 10.1002/hsr2.978
- Rhoades R, Solomon S, Johnson C, Teng S. Impact of SARS-coV-2 on host factors involved in mental disorders. *Front Microbiol.* (2022) 13:845559. doi: 10.3389/fmicb.2022.845559