REVIEW

Understanding the role of serotonin in psychiatric diseases
[version 1; peer review: 3 approved]

Donatella Marazziti
Dipartimento di Medicina Clinica e Sperimentale, Section of Psychiatry, University of Pisa, Via Roma, 67, 56100 Pisa, Italy

Abstract
Serotonin (5-HT) continues to attract researchers’ interest after almost a century. However, despite these efforts, its role has not yet been fully elucidated. It is now evident that 5-HT does not modulate single functions but rather a multiplicity of activities and behaviors present in both normal and several pathological conditions in a less deterministic way than previously assumed. This article aims to briefly review some of the latest advancements in the general role of 5-HT in psychiatry, particularly in depression, and offer the author’s personal reflections.

Keywords
psychiatric disorders, serotonin, pathophysiology, depression

Corresponding author: Donatella Marazziti (dmarazzi@psico.med.unipi.it)
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Introduction
Serotonin (5-HT) is really puzzling. Originally discovered in the blood and in entero-cromaffin cells and first thought to be a vasoconstrictor agent, 5-HT was also described after about twenty years in the central nervous system (CNS), where it is now considered to represent one of the most diffuse, most influential, and probably most investigated neurotransmitters. However, in spite of decades of research all over the world, its nature remains elusive and its role is still surrounded by mystery.

Undoubtedly, the amount of data relative to 5-HT has permitted investigators to describe several aspects of its distribution, physiology, receptor subtypes, mode of functioning, and modulation of different activities in both the CNS and the periphery, including appetite, sleep, mood, sexuality, aggression/impulsivity, biological rhythms, motor control, memory, learning, neuronal degeneration, and gastrointestinal motility and vasoconstriction. In addition, a rich literature shows the involvement of 5-HT in a series of disorders, including almost every neuropsychiatric domain. Indeed, all psychiatric disorders seem to be related to 5-HT dysfunctions, and many, if not all, psychotropic drugs used to treat psychopathological conditions interfere more or less directly with the 5-HT system. However, as we analyze the evolution of hypotheses related to the involvement of 5-HT in the pathophysiology of psychiatric disorders, it is evident that the original enthusiasm based on classic theories, which now appears quite simplistic, has dampened.

Discussion
The investigation of the neurobiology of depression is a clear example of this process and how old theories should be re-conceptualized on the basis of the latest findings. In the 1970s, depression was believed to be due to a deficit of 5-HT neurotransmission. Taken together, convergent data from studies on tryptophan depletion, cerebrospinal fluid levels of 5-hydroxyindolacetic acid, neuroendocrine challenges, autopsy, and peripheral models of presynaptic serotonergic neurons, like platelets, seemed to support the presence of a reduced functioning of the 5-HT system in depression. Interestingly, if we critically analyze those findings, it is evident that negative results were also present since the beginning but were mostly neglected. Moreover, attempts were made to encompass them in the defect hypothesis through rather complicated explanations, sometimes involving the 5-HT transporter (SERT) and one or more of the 5-HT receptor subtypes (of which there are now 14) discovered and characterized throughout the years. Similarly, the function of the genes or genetic polymorphisms that have been continually proposed in depression in the last two decades was not always confirmed sub-tout court that 5-HT is involved in the depressive psychopathology (for example, 30% of depressed patients reach remission from SSRI treatment) or exempt ourselves from exploring other working models. According to the recently emerging role of 5-HT in brain development, it is suggested that early alterations of this process, following environmental stressors or genetic liability, impair brain circuits, pathways, and differentiation and constitute a sort of basic “vulnerability” toward a greater risk of developing psychopathology. In this case, subsequent life events should act through epigenetic mechanisms acting on stress response and emotion regulation. Of interest, both SERT-s allele carriers and sensory processing sensitivity are associated with greater sensitivity to environmental stimuli.
in humans\(^3\). Long-follow-up studies and impact of stressors in childhood and adolescence, together with studies on human DNA methylation or acetylation, should be planned to explore epigenetic mechanisms more thoroughly. It would also be interesting to ascertain whether different types of stressors (familial, emotional, and environmental) should produce different biochemical effects on the 5-HT system, why some individuals become ill and others do not, and what the individual factors promoting resilience are.

Other recent biological hypotheses on the role of 5-HT in depression (and perhaps in all other disorders where serotonergic alterations have been detected) highlight how this neurotransmitter is part of a more complex network including even the immune system and the whole body\(^{26,27}\) or might play a more general role in the energy homeostasis through modulation of mitochondria activity\(^{31}\).

In any case, all research in the 5-HT field might benefit from a deeper knowledge of more precise anatomical data in humans. Undoubtedly, the latest functional magnetic resonance imaging approaches linking brain circuits to SERT-gene polymorphism, emotional processing, and pharmacological challenges appear extremely helpful and promising in this sense\(^{24–26}\).

**Conclusions**

The precise role of 5-HT in psychiatric disorders remains elusive after decades of intensive research. Currently, two main notions are widely accepted in this field. One is that the serotonergic dysfunctions cannot be related to distinct nosological entities but rather to symptoms/dimensions shared by different conditions\(^1\). The second, related to the first, is that the 5-HT hypothesis of psychopathology has become less casual and tends to be more comprehensive, albeit cautious. Therefore, currently, different elements are taken into account when considering the role of 5-HT: its relationships with other neurotransmitters, neuropeptides, and neurotrophins\(^2\) and how it may regulate emotions, cognition, motivation, and behaviors to produce different clinical pictures according to individual vulnerability due to genetic load, life events, and environmental stressors\(^3\).

In 1998, John Greden had already written about 5-HT that “much we have learned” but that there is “So much to discover”\(^33\). After twenty years, we are strongly convinced that “the best is yet to come”, again to quote Greden\(^5\). That is, 5-HT continues (and probably will continue for a long time) to represent a “hot” topic in neuropsychiatry, a real challenge for research, and a “never-ending story”\(^34,35\) that hopefully will permit us to disentangle one of the most fascinating mysteries of our nature and lead to really innovative pharmacological and psychosocial interventions effective in a broad range of psychiatric disorders.

**Abbreviations**

5-HT, serotonin; CNS, central nervous system; SERT, serotonin transporter; SSRI, selective serotonin re-uptake inhibitor.

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**References**

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   *Competing Interests:* No competing interests were disclosed.

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