



The 5-Hydroxytryptamine signaling map: an overview of serotonin-serotonin receptor mediated signaling network

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Received: 11 July 2018 / Accepted: 18 July 2018 / Published online: 24 July 2018
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Abstract

The monoamine neurotransmitter, 5-Hydroxytryptamine or serotonin, is derived from tryptophan and synthesized both centrally and systemically. Fourteen structurally and functionally distinct receptor subtypes have been identified for serotonin, each of which mediates the neurotransmitter's effects through a range of downstream signaling molecules and effectors. Although it is most frequently described for its role in the etiology of neuropsychiatric and mood disorders, serotonin has been implicated in a slew of fundamental physiological processes, including apoptosis, mitochondrial biogenesis, cell proliferation and migration. Its roles as the neurotransmitter have also emerged in pathogenic conditions ranging from anorexia nervosa to cancer. This has necessitated the understanding of the signaling mechanisms underlying the serotonergic system, which led us to construct a consolidative pathway map, which will provide as a resource for future biomedical investigation on this pathway. Using a set of stringent NetPath annotation criteria, we manually curated molecular reactions associated with serotonin and its receptors from publicly available literature; the reaction categories included molecular associations, activation/inhibition, post-translation modification, transport, and gene regulation at transcription and translational level. We identified 90 molecules in serotonin-serotonin receptor pathway. We submitted the curated data to NetPath, a publicly available database of human signaling pathways, in order to enable the wider scientific community to readily access data and contribute further to this pathway.

Keywords NetSlim · Post-translational modification · Protein-protein interaction · Gene expression · Sleep · Serotonylation

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Abbreviations

5-HT	5-Hydroxytryptamine
5-HTR	5-Hydroxytryptamine receptor
CNS	Central nervous system
GPCR	G-protein coupled receptor
TPH	Tryptophan hydroxylase
PTMs	Post-translational modifications
PPIs	Protein-protein interactions
BioPAX	Biological pathway exchange
SBML	Systems biology markup language
PSI-MI	Proteomics standards initiative for molecular interaction

Introduction

The neurotransmitter 5-Hydroxytryptamine (5-HT), or serotonin, is most commonly known for its role in the pathophysiology of various neuropsychiatric disorders. However, an abundance of literature based on serotonergic manipulation

in animal models has yielded knowledge of the plethora of physiological process directly and indirectly influenced by this biogenic monoamine. This is hardly surprising, given that to date seven 5-HT receptor families (5-HT₁₋₇) have been identified. These include 5-HT_{1A, B, D, E, F}; 5-HT_{2A, B, C}; 5-HT₃; 5-HT₄; 5-HT_{5A, B}; 5-HT₆; and 5-HT₇. Barring the 5-HT₃ receptor, which functions as a ligand-gated ion channel (LGIC) (Reeves and Lummis 2002), all other serotonergic receptors mediate their actions via G proteins. By coupling to G α_i , G $\alpha_{q/11}$, or G α_s , the 5-HT receptors are able to exert their influence on several biochemical pathways that are much further downstream.

Serotonin is synthesized via a two-step metabolic pathway: tryptophan is first hydroxylated to 5-hydroxytryptophan (5-HTP) by tryptophan hydroxylase (TPH), which is a rate-limiting step. This is followed by the decarboxylation of 5-HTP by aromatic L-acid decarboxylase to finally form 5-HT (El-Merahbi et al. 2015). Serotonin acts as a neurotransmitter within the central nervous system (CNS), where it is synthesized by raphe neurons in the brain stem; peripherally it can play multiple roles as a hormone, auto- or paracrine factor, and synthesized by both gut neurons and enterochromaffin cells located in the gastrointestinal system (Jenkins et al. 2016). The blood-brain barrier keeps systemic and central serotonin pools distinct.

The serotonin transporter (SERT) is responsible for the reuptake of free 5-HT in the synaptic cleft; this is, in fact, the mechanism of action exploited by selective serotonin reuptake inhibitors (SSRIs), typically used as antidepressants or anxiolytic therapy. By blocking the recapture of 5-HT molecules by SERT, SSRIs increase extracellular 5-HT concentration. The pharmacological focus on the role of 5-HT in the CNS is particularly significant, given that approximately 90–95% of the body's 5-HT is actually localized to the periphery, thus forming the base for the majority of serotonergic influences (Mohammad-Zadeh et al. 2008). Serotonergic signaling has received particular emphasis within the context of neuropsychiatry since the pharmacological manipulation of 5-HT has provided clinicians with significant gains in the treatment of mood disorders.

Serotonin has also been implicated in the regulation of an array of biological functions both within and outside the CNS. Within the CNS, 5-HT is involved in the regulation of mood and social cognition (Jenkins et al. 2016), neurogenesis (Alenina and Klempin 2015), and memory (Nikoui et al. 2016). Serotonergic dysregulation has been linked to numerous psychological conditions, particularly major depressive disorder (Salomon and Cowan 2013). In the periphery, 5-HT has been routinely implicated in the mitogenesis and proliferation of fibroblast cells (Welsh et al. 2004). It also contributes to metabolic homeostasis by regulating the activity of organs involved in glucose and lipid metabolism (El-Merahbi et al. 2015). Several studies have also demonstrated the robust

influence of 5-HT on augmented arterial contraction in cardiac disease and its effects on cardiac hypertrophy (Matsumoto et al. 2010; Vindis et al. 2010). Serotonergic signaling has also been implicated in bronchoconstriction (Hershenson et al. 1995) and the control of rhythmic breathing (Manzke et al. 2010).

While a complete review of the physiological influences of 5-HT and its receptors is beyond the scope of the present study, we attempted to summarize significant and frequently replicated findings. Given the multitude of implications for 5-HT in both physiological and pathogenic processes and its central and systemic presence, a detailed pathway map collating the experimental data available will augment the understanding of this signal transduction network. To the best of our knowledge, an easily accessible and integrative depiction of 5-HT signaling is currently not available, and, therefore, the present study attempted to address this. A systematic effort to catalog the molecules involved in this pathway may help shed new light on the underlying mechanisms involved and add to the translational value of this information, including the accelerated discovery of new therapeutic targets.

Methodology

We conducted an exhaustive literature review of all the studies available on PubMed that examined the downstream effects of both endogenous and synthetic ligand binding to the various 5-HTRs. Only original studies, as opposed to reviews, were considered. Articles were carefully manually screened for ligand-evoked reactions that could be categorized into the following groups: 1) molecular association (protein-protein interactions), 2) post-translational modification (PTM), 3) translocation/transport of proteins between subcellular compartments, 4) protein expression, 5) activation/inhibition, and, finally, 6) gene regulation at the mRNA and/or protein level (both up- and down-regulation). This categorization strictly adhered to the annotation criteria previously outlined in the studies examining BDNF/p75NTR (Sandhya et al. 2013), Oncostatin M (Dey et al. 2013), oxytocin-oxytocin receptor (Chatterjee et al. 2016), interleukin-17 (Sharma et al. 2015), and FGF-1/FGFR (Raju et al. 2014) pathways. Pathbuilder, an in-house annotation tool, was utilized for the annotation of categorized reactions (Kandasamy et al. 2009). Individual molecular reactions were connected via hyperlink to the original PubMed article from which they were sourced.

Our annotation also includes a brief comment about the annotation reaction as well as about the physiological models within which they were observed (e.g., cell lines, transgenic animals, tissue). An instructive pathway map was generated using PathVisio, an open source, free pathway drawing tool (van Iersel et al. 2008). The map provides a pictorial summary of all the reactions annotated, including downstream effectors at both the transcriptional and translational level. Annotated

pathway reactions were exported to the NetPath database, an in-house developed pathway resource (Kandasamy et al. 2010). A designated pathway authority (an established expert in subject-matter) carefully reviewed the constructed pathway map, and the annotation reactions upon which it was based.

Results

Our initial search on PubMed retrieved around 7500 articles that met one or more of the parameters stipulated in our query term. Of these around 206 articles were selected for further curation, based on their fulfillment of all our annotation criteria. The annotated articles yielded a total of 23 molecular association reactions, 84 PTM reactions, 43 activation/inhibition reactions, 32 protein translocation reactions, and 112 gene regulation reactions at transcriptional level and 105 at translational level. Each of these reactions was integrated into a representative map of the signaling pathway (Fig. 1). The NetPath database includes all 5-HT: 5-HT receptor-related signaling events and associated statistics and is freely available to members of the scientific community (http://www.netpath.org/pathways?path_id=NetPath_86). All information is presented in standard community exchange formats, namely Biological Pathway eXchange (BioPAX) (Demir et al. 2010), Systems Biology Markup Language (SBML) (Hucka et al. 2003), and Proteomics Standards Initiative Molecular Interaction (PSI-MI) (Orchard and Kerrien 2010).

As stated elsewhere (Millan et al. 2008) and as demonstrated by our map, it is apparent that there are no “absolute” demarcations between the transduction mechanisms employed by different 5-HT receptor subtypes. We also observed that stimulation of 5-HT receptors with 5-HT induces a similar pattern of enrichment of downstream signaling modules, such as MEK/MAPK, PI3K/AKT, Ras/Raf, and RhoA/ROCK, across all the 5-HT receptors. Our map indicates that

several biological processes may be influenced by the combinatorial effect of several receptors, as opposed to being controlled by a singular receptor. For instance, we observed that activation of 5-HT1, 5-HT2 or 5-HT6 receptors are involved in suppression of apoptotic proteins, such as CASP3 and CASP9, via MEK/MAPK or PI3K/AKT signaling module (Hsiung et al. 2005; Nebigil et al. 2003; Wang et al. 2014). Similarly, cell proliferation was regulated by the AKT/mTOR and MEK/MAPK pathways by both the 5-HT1 and 5-HT2 receptors. It should be noted that activation of the JAK/STAT pathway was only evident for the 5-HT2 receptor (Banes et al. 2005).

We noted that certain biological processes tended to be regulated by specific subtypes; for instance the 5-HT1 and 5-HT7 receptors was found to be involved in the modulation of ion channel activity, which subsequently affected fundamental events, including respiration and synaptic transmission (Vasefi et al. 2013; Cai et al. 2002; Manzke et al. 2010). The 5-HT2 receptor was predominantly involved in the pathogenesis of cardiac hypertrophy and cardiac growth/remodeling via the secretion of NPPA/NPPB and RCAN1 proteins (Liang et al. 2006; Bush et al. 2004).

Interestingly, we see a complex system of cross-talk emerge between the different receptor subtypes and, curiously, across different neurotransmitter systems as well. For instance, a coherent action of 5-HT2 and 5-HT7 receptor in the macrophage polarization process (de Las and Corbi 2014). Also, 5-HT can functionally compensate for the lesion-mediated loss of striatal dopamine and can mitigate glutamate mediated excitotoxicity (Brown and Gerfen 2006; Wang et al. 2006). The physiological and pathological effects of serotonin reflect this complexity, as the serotonergic system is implicated in a range of conditions, including cancer, anorexia nervosa, atherosclerosis, cardiac hypertrophy, and several mood disorders.

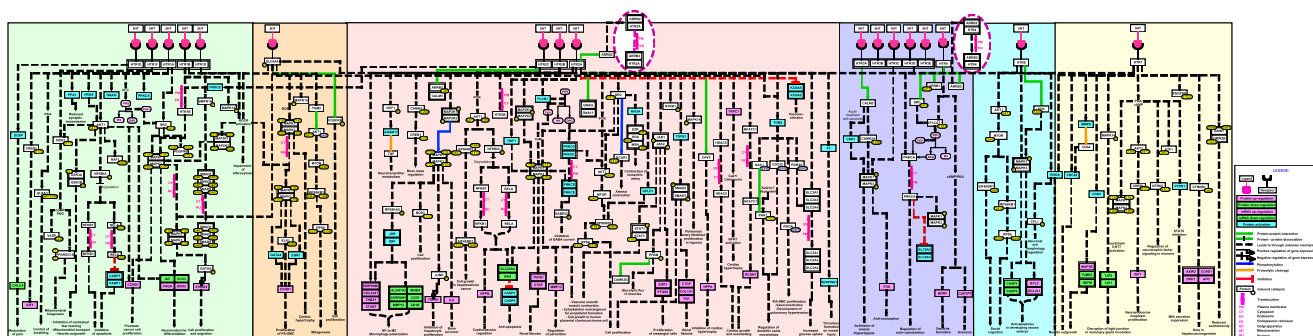


Fig. 1 A schematic representation of the NetPath reactions induced by serotonin-serotonin receptor. The pathway reaction map depicts molecular events induced through serotonin-serotonin receptor interaction. Pathway map represents protein-protein associations,

enzyme catalysis reactions, translocation events, gene and/or protein regulation induced upon treatment with serotonin or its analogues. Legends describe the reaction events in the map

Conclusions

The increasing availability of cell signaling data pertaining to serotonin-serotonin receptor signaling has warranted the systematic cataloging, identification, and characterization of the molecular components involved in the signal transduction of this biogenic amine. Availability of serotonin-serotonin receptor signaling through a centralized system will facilitate understanding of the mammalian serotonergic system. It will also help in understanding regulation and function of this pathway in normal and pathological condition, thereby enabling the formulation of hypotheses that can also be rigorously tested. Researchers can contribute to further characterization of the pathway by sharing their insights in the NetPath comments section (<http://www.netpath.org/comments>).

Acknowledgements We thank Karnataka Biotechnology and Information Technology Services (KBITS), Government of Karnataka for the support to the Center for Systems Biology and Molecular Medicine at Yenepoya (Deemed to be University) under the Biotechnology Skill Enhancement Programme in Multiomics Technology (BiSEP GO ITD 02 MDA 2017). We thank the Department of Biotechnology (DBT), Government of India for research support to the Institute of Bioinformatics (IOB), Bangalore. We thank the “Infosys Foundation” for research support to IOB. LG, OC and PM are recipients of DST INSPIRE Fellowship from the Department of Science and Technology (DST), Government of India. JA is recipient of Senior Research Fellowship from the Council of Scientific and Industrial Research (CSIR), Government of India.

Compliance with ethical standards

Conflict of interest The author(s) declare no conflicts of interests.

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