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Serotonin in the Frontal Cortex: A Potential Therapeutic Target for Neurological Disorders

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Serotonin or 5-hydroxytryptamine (5-HT) is a monoamine neurotransmitter which has broad distribution in the brain. It was discovered by Erspamer and Asero in the 1950s [1]. 5-HT is synthesized in two steps, with Tryptophan Hydroxylase (TPH) as the rate-limiting enzyme [2]. First, tryptophan is converted to 5-hydroxytryptophan (5-HTP) by TPH. Second, the intermediate product, 5-HTP, is converted to 5-HT by aromatic acid decarboxylase (AADC). 5-HT is primarily degraded by the mitochondrial bound protein Monoamine Oxidase A (MAOA), leading to the generation of the metabolite, 5-hydroxyindoleacetic acid (5-HIAA). Importantly, serotonin is also a substrate for melatonin synthesis [3]. 5-HT is released from the axonal terminals of serotonergic neurons and acts on 14 distinct receptor subtypes that are classified into 7 different families: 5-HT₁ (1A, 1B, 1D, 1E, 1F), 5-HT₂ (2A, 2B, and 2C), 5-HT₃, 5-HT₄, 5-HT₅ (5A, 5B), 5-HT₆, and 5-HT₇. Among all these receptors, only 5-HT₃ receptor is a pentameric ligand-gated ion channel composed of several subunits of which 5 different types have been identified [4]. All other 5-HT receptors are G-protein coupled receptors which regulate the activity of the neurons expressing them [5,6]. Released serotonin is transported to the presynaptic neurons by serotonin transporter (SERT or 5-HTT), a type of monoamine transporter protein [7].

Serotonergic neurons are located in the raphe nuclei [8]. While the more caudal raphe nuclei project to the Peripheral Nervous System (PNS), the neurons in the dorsal and median raphe nuclei (DRN and MRN) primarily send their projections to forebrain regions [9,10]. 5-HT is critically involved in the development of many cortices, such as somatosensory cortex and barrel cortex [11,12]. In adult brain, 5-HT neurons project to majority of cortical areas, including the entorhinal and cingulate cortices. However, of all cortical regions, the frontal lobe contains the highest density of serotonergic terminals and 5-HT receptors [13]. These studies indicate that 5-HT regulates cognitive and emotional functions that rely on frontal cortical activity.

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Serotonin homeostasis in the frontal cortex is important for normal behavior. It has been shown that engaging in aggressive behavior triggers dynamic changes in frontal cortical serotonin [14]. Deviation of 5-HT homeostasis increases impulsivity [15–17]. Selective depletion of 5-HT in monkey frontal cortex impairs reversal learning and increases perseveration (loss of cognitive flexibility) [18,19]. 5-HT in the frontal cortex also modulates attention in humans [20,21]. Given its involvement in cognition and impulsivity, 5-HT is central to our understanding of the psychopathology and treatment of psychiatric disorders such as depression, schizophrenia, Obsessive Compulsive Disorder (OCD), and autism. In all of these disorders, local abnormalities in frontal cortex structure [22], neurochemistry [23], or activation [24] have been characterized and drugs for these disorders, such as ecstasy [25] and amphetamine [26], have been shown to impair cortical 5-HT neurotransmission. Moreover, Clarke et al. [18] used a serial discrimination reversal paradigm to show that selective depletion of 5-HT in the marmoset frontal cortex produced perseverative responding to the stimulus previously paired with reward without any significant effects on either retention of a discrimination learned preoperatively or acquisition of a novel discrimination postoperatively. This result highlights the importance of prefrontal serotonin in behavioral flexibility which is highly relevant to obsessive-compulsive disorder, schizophrenia, and the cognitive sequelae of drug abuse in which perseveration is prominent. More interestingly, 5-HT is very likely to be the common neurochemical factor between depression and autism as comorbidity of these two disorders is common [27]. Indeed, selective serotonin reuptake inhibitors (SSRIs) are being increasingly used in autism, because of their role in the control of depression and aggression [27–29].

Furthermore, high-frequency electrical stimulation of the Ventral Medial Prefrontal Cortex (vmPFC) is capable of enhancing 5-HT release and restoring social approach behaviour in defeated mice [30]. Additionally, manipulating vmPFC synaptic inputs to the DRN has revealed bidirectional effects on socioaffective behaviours via direct monosynaptic excitation and indirect disynaptic inhibition of 5-HT neurons [31]. Similarly, deep brain stimulation in the vmPFC improves negative bias and symptoms of mood dysregulation in Major Depressive Disorder (MDD) patients [32]. Strikingly, these results suggest that cross-species parallels exist in regards to the roles of the frontal cortex and serotonergic systems in socioaffective responses. It has been hypothesized that the plasticity of the frontal cortex-DRN circuit that links these two systems may constitute a conserved means of encoding or expressing social avoidance behaviour across species [31]. Thus, better understanding the interaction between frontal cortex and DRN and identifying key neuroplastic events that mediate normal and pathological regulation of socioaffective functions may uncover molecular targets amenable to therapeutic intervention in the treatment of affective disorders.

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References

1. Erspamer V, Asero B. Identification of enteramine, the specific hormone of the enterochromaffin cell system, as 5-hydroxytryptamine. *Nature*. 1952; 169:800–801.
2. Fitzpatrick PF. Tetrahydropterin-dependent amino acid hydroxylases. *Ann Rev Biochem*. 1999; 68:355–381. [PubMed: 10872454]
3. Muller CL, Anacker AM, Veenstra-VanderWeele J. The serotonin system in autism spectrum disorder: From biomarker to animal models. *Neuroscience*. 2016; 321:24–41. [PubMed: 26577932]
4. Kilpatrick GJ, Bunce KT, Tyers MB. 5-HT₃ receptors. *Med Res Rev*. 1990; 10:441–475. [PubMed: 2243511]
5. Hannon J, Hoyer D. Molecular biology of 5-HT receptors. *Behav Brain Res*. 2008; 195:198–213. [PubMed: 18571247]
6. Millan MJ, Marin P, Bockaert J, La Cour CM. Signaling at G-protein-coupled serotonin receptors: recent advances and future research directions. *Trend Pharmacol Sci*. 2008; 29:454–464.
7. Wolf WA, Kuhn DM. Modulation of serotonin release. Interactions between the serotonin transporter and autoreceptors. *Ann N Y Acad Sci*. 1990; 604:505–513. [PubMed: 2171405]
8. Dahlstroem A, Fuxe K. Evidence for the Existence of Monoamine-Containing Neurons in the Central Nervous System. I. Demonstration of Monoamines in the Cell Bodies of Brain Stem Neurons. *Acta Physiol Scand Suppl*. 1964; 232:231–255.
9. Conrad LC, Leonard CM, Pfaff DW. Connections of the median and dorsal raphe nuclei in the rat: an autoradiographic and degeneration study. *J Comp Neurol*. 1974; 156:179–205. [PubMed: 4419253]
10. O'Hearn E, Molliver ME. Organization of raphe-cortical projections in rat: a quantitative retrograde study. *Brain Res Bull*. 1984; 13:709–726. [PubMed: 6099744]
11. Lidow MS, Rakic P. Scheduling of monoaminergic neurotransmitter receptor expression in the primate neocortex during postnatal development. *Cereb Cortex*. 1992; 2:401–416. [PubMed: 1330122]
12. Bonnin A, Peng W, Hewlett W, Levitt P. Expression mapping of 5-HT₁ serotonin receptor subtypes during fetal and early postnatal mouse forebrain development. *Neuroscience*. 2006; 141:781–794. [PubMed: 16824687]
13. Celada P, Puig MV, Artigas F. Serotonin modulation of cortical neurons and networks. *Front Integr Neurosci*. 2013; 7:25. [PubMed: 23626526]
14. Miczek KA, Fish EW, De Bold JF, De Almeida RM. Social and neural determinants of aggressive behavior: pharmacotherapeutic targets at serotonin, dopamine and gamma-aminobutyric acid systems. *Psychopharmacology*. 2002; 163:434–458. [PubMed: 12373445]
15. Harrison AA, Everitt BJ, Robbins TW. Central 5-HT depletion enhances impulsive responding without affecting the accuracy of attentional performance: interactions with dopaminergic mechanisms. *Psychopharmacology*. 1997; 133:329–342. [PubMed: 9372531]
16. Dalley JW, Theobald DE, Eagle DM, Passetti F, Robbins TW. Deficits in impulse control associated with tonically-elevated serotonergic function in rat prefrontal cortex. *Neuropsychopharmacology*. 2002; 26:716–728. [PubMed: 12007742]
17. Anderson GL, Limacher M, Assaf AR, Bassford T, Beresford SA, et al. Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: the Women's Health Initiative randomized controlled trial. *JAMA*. 2004; 291:1701–1712. [PubMed: 15082697]
18. Clarke HF, Dalley JW, Crofts HS, Robbins TW, Roberts AC. Cognitive inflexibility after prefrontal serotonin depletion. *Science*. 2004; 304:878–880. [PubMed: 15131308]
19. Clarke HF, Walker SC, Crofts HS, Dalley JW, Robbins TW, et al. Prefrontal serotonin depletion affects reversal learning but not attentional set shifting. *J Neurosci*. 2005; 25:532–538. [PubMed: 15647499]
20. Carter OL, Burr DC, Pettigrew JD, Wallis GM, Hasler F, et al. Using psilocybin to investigate the relationship between attention, working memory, and the serotonin 1A and 2A receptors. *J Cogn Neurosci*. 2005; 17:1497–1508. [PubMed: 16269092]

21. Scholes KE, Harrison BJ, O'Neill BV, Leung S, Croft RJ, et al. Acute serotonin and dopamine depletion improves attentional control: findings from the stroop task. *Neuropsychopharmacology*. 2007; 32:1600–1610. [PubMed: 17151596]
22. Baare WF, Hulshoff Pol HE, Hijman R, Mali WP, Viergever MA, et al. Volumetric analysis of frontal lobe regions in schizophrenia: relation to cognitive function and symptomatology. *Biol Psychiatr*. 1999; 45:1597–1605.
23. Insel TR, Winslow JT. Neurobiology of obsessive compulsive disorder. *Psychiatr Clin North Am*. 1992; 15:813–824. [PubMed: 1461798]
24. Mayberg HS, Brannan SK, Mahurin RK, Jerabek PA, Brickman JS, et al. Cingulate function in depression: a potential predictor of treatment response. *Neuroreport*. 1997; 8:1057–1061. [PubMed: 9141092]
25. McCann UD, Eligulashvili V, Ricaurte GA. (+/-)3,4-Methylenedioxymeth-amphetamine ('Ecstasy')-induced serotonin neurotoxicity: clinical studies. *Neuropsychobiology*. 2000; 42:11–16.
26. Wilson JM, Kalasinsky KS, Levey AI, Bergeron C, Reiber G, et al. Striatal dopamine nerve terminal markers in human, chronic methamphetamine users. *Nat Med*. 1996; 2:699–703. [PubMed: 8640565]
27. Ghaziuddin M, Ghaziuddin N, Greden J. Depression in persons with autism: implications for research and clinical care. *J Autism Dev Disord*. 2002; 32:299–306. [PubMed: 12199134]
28. DeLong GR, Teague LA, McSwain Kamran M. Effects of fluoxetine treatment in young children with idiopathic autism. *Dev Med Child Neurol*. 1998; 40:551–562. [PubMed: 9746008]
29. Ghaziuddin M, Tsai L, Ghaziuddin N. Fluoxetine in autism with depression. *J Am Acad Child Adolesc Psychiatry*. 1991; 30:508–509.
30. Hamani C, Diwan M, Macedo CE, Brandao ML, Shumake J, et al. Antidepressant-like effects of medial prefrontal cortex deep brain stimulation in rats. *Biol Psychiatry*. 2010; 67:117–124. [PubMed: 19819426]
31. Challis C, Berton O. Top-Down Control of Serotonin Systems by the Prefrontal Cortex: A Path toward Restored Socioemotional Function in Depression. *ACS Chem Neurosci*. 2015; 6:1040–1054. [PubMed: 25706226]
32. Veerakumar A, Challis C, Gupta P, Da J, Upadhyay A, et al. Antidepressant-like effects of cortical deep brain stimulation coincides with proneuroplastic adaptations of serotonin systems. *Biol Psychiatry*. 2014; 76:203–212. [PubMed: 24503468]