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The serotonin 5-HT3 receptor: a novel neurodevelopmental target

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In addition to its role as a classical neurotransmitter, it is now well established that serotonin (5-hydroxytryptamine, 5-HT) plays a pivotal role in the development of the mammalian central nervous system (CNS). 5-HT is one of the first neurotransmitters to appear during development (E13 in the rat, Lauder, 1990; and E11 in the mouse, Pfaf et al., 2002) and acts as a neurotrophic factor in early embryonic CNS development and thus even before synapse formation of cortical neurons is completed. Therefore, it aids in establishing CNS organization, supporting as well serotoninergic synapses in the developing brain including a ligand-gated ion channel, the 5-HT3 receptor. Over the past years, evidence has been accumulating that 5-HT3 receptors are involved in the regulation of neurodevelopment by serotonin. Here, we review the spatial and temporal expression patterns of 5-HT3 receptors in the pre- and early postnatal rodent brain and its functional implications. First, 5-HT3 receptors are expressed on GABAergic interneurons in neocortex and limbic structures derived from the caudal ganglionic eminence. Mature inhibitory GABAergic interneurons fine-tune neuronal excitability and thus are crucial for the physiological function of the brain. Second, 5-HT3 receptors are expressed on specific glutamatergic neurons, Cajal–Retzius cells in the cortex and granule cells in the cerebellum, where they regulate morphology, positioning, and connectivity of the local microcircuitry. Taken together, the 5-HT3 receptor emerges as a potential key-regulator of network formation and function in the CNS, which could have a major impact on our understanding of neurodevelopmental disorders in which 5-HT plays a role.

Keywords: serotonin, 5-HT3 receptor, development, interneurons, neuroblasts

INTRODUCTION

In addition to its role as a classical neurotransmitter, it is now well established that serotonin (5-hydroxytryptamine, 5-HT) plays a pivotal role in the development of the mammalian central nervous system (CNS). 5-HT is one of the first neurotransmitters to appear during development (E13 in the rat, Lauder, 1990; and E11 in the mouse, Pfaf et al., 2002) and acts as a neurotrophic factor in early embryonic CNS development and thus even before synapse formation of cortical neurons is completed. Therefore, it aids in establishing CNS organization, supporting as well serotoninergic synapses in the developing brain including a ligand-gated ion channel, the 5-HT3 receptor. Over the past years, evidence has been accumulating that 5-HT3 receptors are involved in the regulation of neurodevelopment by serotonin. Here, we review the spatial and temporal expression patterns of 5-HT3 receptors in the pre- and early postnatal rodent brain and its functional implications. First, 5-HT3 receptors are expressed on GABAergic interneurons in neocortex and limbic structures derived from the caudal ganglionic eminence. Mature inhibitory GABAergic interneurons fine-tune neuronal excitability and thus are crucial for the physiological function of the brain. Second, 5-HT3 receptors are expressed on specific glutamatergic neurons, Cajal–Retzius cells in the cortex and granule cells in the cerebellum, where they regulate morphology, positioning, and connectivity of the local microcircuitry. Taken together, the 5-HT3 receptor emerges as a potential key-regulator of network formation and function in the CNS, which could have a major impact on our understanding of neurodevelopmental disorders in which 5-HT plays a role.

EXPRESSION OF 5-HT3 RECEPTORS DURING DEVELOPMENT

The 5-HT3 receptor belongs, together with the nicotinergic acetylcholine, the GABAA receptor, and the glycine receptor, to the Cys-loop family of ligand-gated ion channels (Barnes and Sharp, 1999; Chameau and van Hooft, 2006; Walstab et al., 2010; Lummis, 2012). To date, two subunits (5-HT3A and 5-HT3B) have been identified in rodents (Martin et al., 1995; Davies et al., 1999), and additional three subunits (κ–η) have been identified in humans (Niesler et al., 2007). Functional 5-HT3 receptors can be built from the same (only 5-HT3A) or different subunits (5-HT3A and 5-HT3B receptor subunits). The receptor composition is crucial for its function (Chameau and van Hooft, 2006;...
In the CNS, the 5-HT$_3$ receptor is first observed in the subpallial ganglionic eminence (GE), the major source of interneurons in the basal telencephalon, at E12.5 (Johnson and Heinemann, 1995; Miquel et al., 1995; Tecott et al., 1995). The rodent GE generates later neocortical GABAergic interneurons which migrate tangentially into the cortical plate. In contrast, neocortical glutamatergic neurons originate in the pallial ventricular zone (VZ) and migrate radially into the cortex (Corbin et al., 2001; Nadarajah and Parnavelas, 2002). Different areas of the GE give rise to various subpopulations of GABAergic interneurons which can be subclassified by their morphology and neuropeptide expression (Flames and Marin, 2005; Rudy et al., 2011; Vitalis and Rossi, 2011).

5-HT$_3$ receptor-positive interneurons compromise ~30% of the superficial GABAergic interneurons in the somatosensory cortex (Lee et al., 2010). They express cholera toxin subunit A (CT), vasoactive intestinal peptide (VIP), and/or neuropeptide Y (NPY) and, at smaller fractions, calretinin (CR) and/or reelin, but not parvalbumin (PV) or somatostatin (SST; Morales and Bloom, 1997; Ferreira et al., 2002; Inta et al., 2008; Lee et al., 2010; Vucurovic et al., 2010). Further expressing several morphological and electrophysiological properties, 5-HT$_3$ receptor-positive interneurons form a rather heterogeneous group of cells, whose potential common properties remain to be fully characterized (for a recent review, see Rudy et al., 2011). 5-HT$_3$ receptor-expressing neocortical interneurons are not only excited by 5-HT but also acetylcholine via nicotinic receptors (Lee et al., 2010; Vucurovic et al., 2010). Additionally, they migrate into the neocortical layers in an “outside-in” manner (Vucurovic et al., 2010) rather than the “inside-out” integration manner of PV- and SST-expressing interneurons. Such “outside-in” neurogenesis was previously described as a feature of CR interneurons (Rymar and Sadikot, 2007). Interestingly, in contrast to PV-interneurons, the birthdate of these CR-expressing interneurons does not match that of neighboring projection neurons in the corresponding layer (Vucurovic et al., 2004; Rymar and Sadikot, 2007). This might be true as well for the 5-HT$_3$ receptor-positive interneurons. Therefore, 5-HT$_3$ receptor-expressing CGE-derived neocortical interneurons might form a group of cells with very specific, yet unknown, characteristics and might follow different migration- and integration cues than other major groups of interneurons like PV-positive interneurons (Lee et al., 2010; Miyoshi et al., 2010).

In grafting experiments, Vucurovic et al. (2010) found that CGE-derived cells also populated several limbic structures including the bed nucleus of the stria terminalis, anterior amygdaloid area, and hippocampus. These were derived earlier from the CGE than the neocortical cells, which is in line with earlier genesis of interneurons in these regions (Vucurovic et al., 2010).

Furthermore, next to the CGE, embryonic 5-HT$_3$ receptor expression was also observed in cells of the entopallial area (AEP) and peripallial area (POA; Lee et al., 2010; Vucurovic et al., 2010). The further development of these cells has not been characterized yet. Cells from the POA might contribute to interneurons in the neocortex (Gelman et al., 2009, 2011) and thus it was proposed that the POA might also give rise to 5-HT$_3$ receptor-positive interneurons of the neocortex (Rudy et al., 2011). However, Vucurovic et al. (2010) found no evidence of POA cells migrating into neocortical regions but the cells rather contributed,
dependent on their birthdate, to cells of the dentate gyrus (DG), amygdala, endopiriform nucleus, and the claustrum.

**5-HT3 RECEPTORS ARE EXPRESSED IN POSTNATAL IMMATURE NEURONS**

5-HT3 receptors are expressed in migrating neuroblasts in several migratory streams derived from the SVZ in the early postnatal brain (Inta et al., 2008; Vucurovic et al., 2010). The SVZ, and therefore these neuroblasts, are not derived from the CGE but from the lateral GE (LGE). Migratory streams in the early postnatal rodent brain are part of the ongoing neurogenesis and migration of neurons after birth. These migratory streams include the rostral migratory stream (RMS) populating mainly the olfactory bulb (OB), the dorsal migratory pathway (DMP) above the hippocampal and optical neuromeres directed toward the cortical axis, the entopeduncular migratory pathway (VMP) heading toward the striatum and nucleus accumbens, and the external migratory pathway (EMP) aiming toward lateo-dorsal brain regions (Inta et al., 2008). Neuroblasts of the RMS do not only migrate into and mature within the OB but also integrate into the cortex (Le Magueresse et al., 2011). Next to cortical interneurons derived from embryonic interneuron genesis, these neuroblasts mature into a novel, recently described subclass of CR-positive interneurons with unique firing pattern (“small axonless neurons”) which are uniquely generated in the early postnatal period and mainly integrate into deeper layers of olfactory and orbital cortices (Le Magueresse et al., 2011). Additionally, 5-HT3 receptor-positive postnatal SVZ-derived neuroblasts, so-called immature white matter interstitial cells, were recently described to populate the corpus callosum (von Engelhardt et al., 2011).

Of the several postnatal migratory streams harboring 5-HT3 receptor-positive neuroblasts, only the RMS persists into adulthood as an area of secondary neurogenesis (Alvarez-Buylla and Garcia-Verdugo, 2002; Abrous et al., 2005) containing 5-HT3 receptor-positive neuroblasts (Inta et al., 2008; Chen et al., 2012). Similar to early postnatal RMS neuroblasts, they migrate and integrate into the OB, where they mature to CR- and VIP-positive but calbindin- (CB) negative interneurons. Interestingly, in contrast to cortical interneurons derived from the CGE, about one-third and one-tenth of the 5-HT3 receptor-expressing interneurons in the OB are PV- and SST-positive, respectively (Chen et al., 2012). Adult SVZ neurogenesis is of particular clinical interest because SVZ-derived neuroblasts can migrate into the cortex upon traumatic events or in neurodegenerative diseases to replace cortical neurons. Indeed, upon stroke in adult mice 5-HT3 receptor-positive neuroblasts migrate into the cortex and mature to CR-positive interneurons (Kreuzberg et al., 2010). However, the majority of these cells loses 5-HT3 receptor expression upon maturation (Kreuzberg et al., 2010).

To conclude, 5-HT3 receptor-expressing neuroblasts are present in several locations in the early postnatal and adult brain.

Next to the pre- and postnatal central expression of 5-HT3 receptors on mature and immature interneurons, recent evidence showed also expression on two specific types of glutamatergic cells: cerebellar granule cells and cortical Cajal–Retzius cells. First, ubiquitous post-/extra- and presynaptic expression of 5-HT3 receptors was recently observed in glutamatergic granule cells of the cerebellum within the first three postnatal weeks in rodents (Oostland et al., 2011, 2013). 5-HT3 receptors are important for the serotonergic regulation of short-term synaptic plasticity at parallel fiber-Purkinje cell synapses during the early postnatal sensitive period and regulate the maturation state of these synapses (Oostland et al., 2011). They further regulate the

**CONCLUSION I: 5-HT3 RECEPTORS ARE A POTENTIAL CENTRAL PART OF MATURATING INTERNEURONS DURING PRE- AND POSTNATAL CORTICAL DEVELOPMENT**

Next to the pre- and postnatal central expression of 5-HT3 receptors on mature and immature interneurons, recent evidence showed also expression on two specific types of glutamatergic cells: cerebellar granule cells and cortical Cajal–Retzius cells. First, ubiquitous post-/extra- and presynaptic expression of 5-HT3 receptors was recently observed in glutamatergic granule cells of the cerebellum within the first three postnatal weeks in rodents (Oostland et al., 2011, 2013). 5-HT3 receptors are important for the serotonergic regulation of short-term synaptic plasticity at parallel fiber-Purkinje cell synapses during the early postnatal sensitive period and regulate the maturation state of these synapses (Oostland et al., 2011). They further regulate the
time course of early postnatal morphological maturation of Purkinje cells as indicated by higher dendritic length and complexity in 5-HT$_3$ receptor knock-out mice and in vitro after treatment with a 5-HT$_3$ receptor antagonist (Oostland et al., 2013). 5-HT$_3$ receptor knock-out animals further show delayed climbing-fiber elimination (Oostland et al., 2013). However, morphology and physiology of Purkinje cells in 5-HT$_3$ receptor knock-out mice appears normal in adult mice, thus indicating a narrow postnatal time window of serotonergic, 5-HT$_3$ receptor-mediated regulation of cerebellar maturation and connectivity (Oostland et al., 2013). Further research might explore a function of 5-HT$_3$ receptors in the development of early life motor coordination and learning.
Second, glutamatergic Cajal–Retzius cells were recently described to express 5-HT3 receptors upon birth (Chameau et al., 2009; Lee et al., 2010). Cajal–Retzius cells are transient neurons located in the marginal zones of the neocortex and hippocampus during CNS development (Marín-Padilla, 1998). In the cortex, they are strategically located in layer I, the area where the apical dendrites of pyramidal neurons terminate and secrete the extra-cellular matrix glycoprotein reelin. Reelin plays a major role as guidance factor for cell migration, cell positioning, and neuronal process outgrowth (Frotscher, 1997). Cajal–Retzius cells in mice are innervated by serotonergic fibers as early as E16. Disruption of the serotoninergic system during embryonic development results in lower levels of reelin and a disturbed corticogenesis with disrupted formation of cortical columns (Fusco et al., 2004). The regulation of corticogenesis by Cajal–Retzius cells is at least partly dependent on 5-HT3 receptor signaling (Chameau et al., 2009, Chameau et al. (2009) not only reported expression of 5-HT3 receptors specifically on Cajal–Retzius cells (but not on pyramidal neurons), but further established a novel role of 5-HT3 receptors, Cajal–Retzius cells, and reelin in the postnatal maturation of cortical pyramidal neurons. Cajal–Retzius cells limit the apical dendritic outgrowth of cortical layer II/III pyramidal cells and thus complexity of cytoarchitecture and network formation. Blocking 5-HT3 receptor activity with an antagonist or reelin signaling with an anti-reelin antibody leads to hypercomplexity of the apical dendrites of layer II/III pyramidal neurons in the somatosensory cortex. A similar phenotype is also present in 5-HT3 receptor knock-out mice and can be rescued by application of recombinant reelin (Chameau et al., 2009). However, it remains to be investigated if, and how, the release of reelin from Cajal–Retzius cells is directly regulated by 5-HT3 receptor activity. Similar findings of possibly indirect regulation of reelin and regulation of cytoarchitecture in cortical pyramidal neurons were shown in vitro in mixed GABA- and non-GABAergic cortical neuron cultures, where 5-HT3 receptor activation inhibited axonal and dendritic outgrowth and dendritic branching only in non-GABAAergic cells (Hayashi et al., 2010).

The increased dendritic complexity of cortical layer II/III pyramidal neurons in 5-HT3 receptor knock-out mice has been associated with altered cortical spatial organization and connectivity with larger dendritic bundles in layer III tangential sections, whereas spine density was not affected (Smit-Rigter et al., 2011). On a functional level, the increase in dendritic complexity of cortical layer II/III pyramidal neurons in 5-HT3 receptor knock-out mice results in a different firing pattern of these cells (van der Velden et al., 2012), suggesting that 5-HT3 receptor activity during maturation of neurons is not only important for the wiring of the local microcircuitry, but also consequently for the processing of information within the circuit. As a potential consequence of this disturbed cortical wiring and function, 5-HT3 receptor knock-out mice display reduced anxiety-like behavior (Kelley et al., 2003; Bhattacharjee et al., 2004) and impaired social behavior (Smit-Rigter et al., 2010), although a direct link between the cortical abnormalities and the behavioral phenotypes remains to be established.

CONCLUSION II: 5-HT3 RECEPTORS REGULATE MATURATION AND DENDRITE COMPLEXITY OF NON-INNERVATED CELLS

5-HT3 receptors regulate the wiring of the local microcircuit in the cortex and the cerebellum by yet unknown direct or indirect mechanisms via Cajal–Retzius cells and granule cells, respectively. Therefore, 5-HT3 receptors may be crucially involved in the formation of higher-level neuronal structures (Figure 1).

PUTATIVE IMPLICATIONS FOR NEURODEVELOPMENTAL DISORDERS

5-HT3 receptors are associated with several psychiatric disorders in humans. Single nucleotide polymorphism, especially the C175T polymorphism in the 5′UTR region of the 5-HT3 receptor, were found to be associated with bipolar disorder (Niesler et al., 2001), schizophrenia (Niesler et al., 2001; Thompson et al., 2006), lowered harm avoidance in women (Melke and Westberg, 2003), alcohol and drug dependence (Enoch et al., 2010), lowered activity of amygdala and prefrontal cortex (Bhattacharjee et al., 2005), prefrontal and hippocampal gray matter loss, and early life quality-dependent elevated depressed mood (Gaut et al., 2010a,b). These variants are associated with changes in 5-HT3 receptor function and expression (Krzewiński et al., 2007). However, it has to be noted that 5-HT3 receptor genetics is fundamentally different between humans and rodents. 5-HT3 receptor expression in humans is much more complicated including additional splice variants of 5-HT3α, the possible expression of heteromeric receptors in the CNS, and three additional receptor genes (5-HT3C, –g), whose function and expression in the CNS have yet to be investigated.

The data presented in this review highlights the 5-HT3 receptor as a crucial regulator of brain development. This also makes it interesting as novel candidate to be involved brain development pathologies such as ASD. Indeed, several studies present evidence that ASD might be caused by disruptions of the serotoninergic system during brain development. Common ASD animal models are based on alterations of prenatal 5-HT levels (Whitaker, Armita, 2005; Boylan et al., 2007; Hohmann et al., 2007). Likewise, clinical data from ASD patients points toward a causal relationship of distortion of the serotoninergic system and ASD pathology (Anderson et al., 1987; Naffah-Mazzacoratti et al., 1993; Chugani, 2002).

Investigating a potential role of 5-HT3 receptors in the development of ASD, it is apparent that 5-HT3 receptor knock-out mice display some features similar to ASD symptoms including impaired social behavior (Smit-Rigter et al., 2010) and a reduction in basal anxiety-related behavior (Kelley et al., 2003; Bhattacharjee et al., 2004; Smit-Rigter et al., 2010). Further, in line with the potential role of the 5-HT3 receptor outlined earlier in this review, these animals display some alterations in neocortical development as hypercomplexity of apical dendrites of cortical layer II/III pyramidal neurons (Chameau et al., 2009) and increased apical dendrite bundling (Smit-Rigter et al., 2011). Disruptions of neocortical development, especially in the balance between excitatory and inhibitory circuits, might at least partially underlie autism neurobiology (Polleux and Lauder, 2004; Levitt, 2005).

For example, in parallel with 5-HT3 receptor knock-out animals, ASD patients display a cortical column pathology with changes in cortical minicolumn size, number and cellular distribution,
and increased cortical volume (Bailey et al., 1998; Casanova et al., 2002; Carper and Courchesne, 2005). Further, reelin signaling was proposed to be impaired in ASD (Fitzsimmons et al., 2005). Indeed, 5-HT3 gene polymorphisms were recently found to be associated with ASD (Anderson et al., 2009; Rehnström et al., 2009). However, there is yet no evidence of a role of 5-HT3 receptors in the etiology of ASD.

Finally, recent literature draws attention to the potential risk of disturbing serotonergic circuits during fetal brain development via exposure of fetuses to selective serotonin reuptake inhibitors (SSRIs). The use of SSRIs by pregnant women, especially during the first trimester, may increase the risk of ASD in the offspring (Cronen et al., 2011). In mice, early postnatal exposure to SSRIS leads to increased anxiety-like behavior (Ansorge et al., 2004). In addition, in utero exposure to fluoxetine leads to life-long abnormalities of cortical cytoarchitecture and increased anxiety-like behavior (Smrit-Riger et al., 2012). These findings suggest that 5-HT3 receptor knock-out mice suggesting that the adverse effect of fluoxetine-exposure during brain development might be 5-HT3 receptor-dependent (Smrit-Riger et al., 2012).

We conclude that, although current data is still limited, 5-HT3 receptors are important for proper brain development. The 5-HT3 receptor knock-out mouse has proven to be a valuable tool to elucidate some of the roles of 5-HT3 receptors in neuronal development. However, the availability of more advanced tools to knock-out or -down 5-HT3 receptors in a more spatially and temporally controlled manner is eagerly anticipated.

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