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Role of serotonin in modulating the development and function of adult-born neurons in the olfactory bulb

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The neuromodulatory transmitter serotonin (5-hydroxytryptamine, 5-HT) is synthesized by neurons located in the brainstem, which project more or less densely to the entire central nervous system (Charnay and Leger, 2010). Serotonin regulates a variety of physiological functions, including food intake, reward, reproduction, sleep-wake cycle, memory, cognition, emotion, and mood (Charnay and Leger, 2010). Consistently, dysfunctions of the serotonergic system are involved in the development or progression of mental disorders including autism, insomnia, anxiety, depression, schizophrenia, Parkinson's disease, or Alzheimer's disease (Charnay and Leger 2010). Many of these diseases (e.g., autism, schizophrenia, depression, Parkinson's disease, Alzheimer's disease) present with concomitant impairment of olfaction (and memory), often accompanied by a reduced volume of the olfactory bulb (OB; **Figure 1A**) and hippocampus. These functional impairments may result from distorted adult neurogenesis in the respective neurogenic niches, as OB and hippocampal dentate gyrus are the two major areas of the adult mammalian brain where adult-born cells are generated throughout life. A wide range of studies documents the involvement of adult-born cells in short- and long-term olfactory memory; perceptual, associative, and fear learning, etc. (summarized in Lepousez et al., 2015; Fomin-Thunemann et al., 2020).

Interestingly, adult neurogenesis and olfactory memory are positively modulated by fluoxetine, an antidepressant drug and selective serotonin reuptake inhibitor (Siopi et al., 2016). Cumulative evidence points towards a specific role for serotonin in adult neurogenesis, as it has been shown that serotonin modulates the fate and functional state of adult-born cells throughout the entire life. Serotonergic projections innervate both the hippocampus and OB (Charnay and Leger, 2010), as well as their respective neurogenic niches, the subgranular zone and subventricular zone (SVZ) (Soumier et al., 2010; Garcia-Gonzalez et al., 2017). Serotonergic fibers innervating the OB originate from the dorsal and medial raphe nuclei and primarily innervate the superficial glomerular layer of the OB (**Figure 1B** and **C**), with sparser innervation of granule and mitral cell layers (Petzold et al., 2009; Fletcher and Chen, 2010).

Interestingly, the serotonergic innervation of the glomerular layer of the bulb is not homogeneous, as the density and thickness of innervating serotonergic fibers vary between adjacent glomeruli. Within the neurogenic niche in the SVZ, serotonergic inputs run along the wall of the lateral ventricle (Tong et al., 2014). Here, the radial glia-like cells (B cells) give rise to transient amplifying cells (C cells), which then generate neuroblasts (**Figure 1C**). Serotonin promotes the proliferation of B and C cells in the SVZ (Brezun and Daszuta, 1999; Soumier et al., 2010; Tong et al., 2014). The thymidine analog bromodeoxyuridine (BrdU) is often used for identification of newborn cells, as it incorporates into the DNA of dividing cells and can later be visualized using immunohistochemistry. Lesioning serotonergic terminals or inhibition of serotonin synthesis leads to a substantial decrease in the number of BrdU-positive ($BrdU^+$) adult-born cells in the SVZ (Brezun and Daszuta, 1999), while an infusion of the serotonin-releasing drug fenfluramine into the lateral ventricle of adult mice significantly increases the number of $BrdU^+$ adult-born cells and doublecortin-positive neuroblasts in the SVZ (Tong et al., 2014). Consistently, 5-HT1A and 5-HT2C receptor agonists increased, while 5-HT2C receptor antagonists decreased cell proliferation in the SVZ of adult mice (Tong et al., 2014). Besides, serotonin application induced depolarising inward currents in B cells, which were partially blocked by 5-HT2C or 5-HT5A receptor antagonists. The co-application of 5-HT2C and 5-HT5A receptor antagonists completely abolished serotonin-induced currents in B cells (Tong et al., 2014). Collectively, these data highlight the importance of serotonin in controlling proliferation and neurogenesis in the SVZ.

After leaving the SVZ, adult-born cells - called neuroblasts at this developmental stage - migrate along the RMS towards the OB (**Figure 1B** and **C**). Migrating neuroblasts express Ca^{2+}-permeable 5-HT3A receptors and serotonergic fibers, projecting along the RMS, have been shown to control velocity and directionality of neuroblast migration in a Ca^{2+}-dependent manner (Garcia-Gonzalez et al., 2017). Moreover, a constitutive 5-HT3A receptor knockout presented with thinner RMS, smaller OB, and reduced density of parvalbumin- and calretinin-positive interneurons in the granule cell and the external plexiform layers (see **Figure 1C** for a schematic illustration of the OB layers).

Upon arrival in the OB, neuroblasts change from tangential to radial migration (**Figure 1B** and **C**) and move towards the OB surface to become GABAergic interneurons in the granule or glomerular cell layers. Ninety percent of these cells become granule cells, while 5–10% migrate into the glomerular layer to become periglomerular or to a lesser extent short axon cells (Lepousez et al., 2015). The latter are collectively referred to as juxtaglomerular cells (JGCs). During the pre-integration phase, i.e.

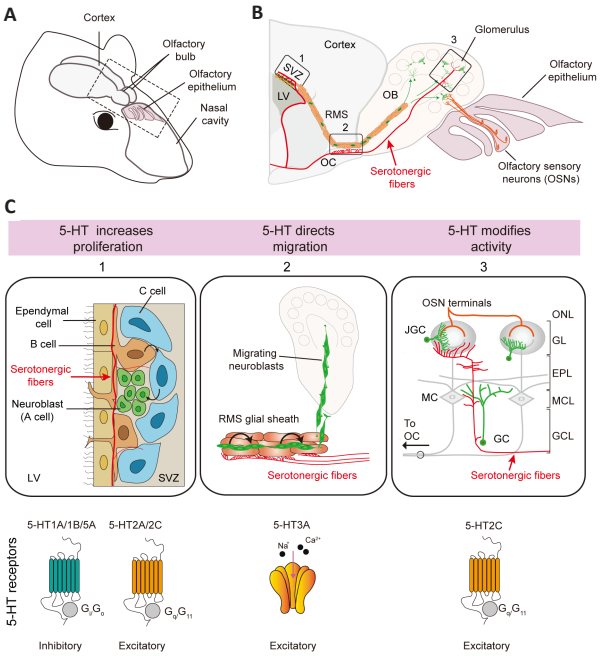

Figure 1 | **Region-specific effects of serotonergic signaling on adult neurogenesis.**
(A) Scheme of the mouse head showing the location of the nasal cavity, olfactory epithelium, olfactory bulb (OB), and the cortex. (B) Magnification of the area, delineated by the broken line in A, showing olfactory sensory neurons (OSNs, orange) within the olfactory epithelium projecting to the OB and terminating in the glomeruli. Adult-born cells (green) arrive in the OB after migration along the rostral migratory stream (RMS) from the subventricular zone (SVZ). Serotonergic fibers (red) originate from the dorsal and medial raphe nuclei in the brain stem and target adult-born cells in the SVZ (1), RMS (2), and OB (3). OC: olfactory cortex; LV: lateral ventricle. (C) Upper panel: close-up of the three framed areas in B. Left: In the SVZ, radial glia-like cells (B cells) give rise to transient amplifying cells (C cells), which then generate neuroblasts (A cells). Middle: in the RMS, neuroblasts migrate along the glial sheets to the OB. After arrival, they switch to radial migration. Right: In the OB, neuroblasts mature to become granule (GCs) and juxtaglomerular (JGCs) cells. EPL: External plexiform layer; GCL: granule cell layer; GL: glomerular layer; MCL: mitral cell layer; ONL: olfactory nerve layer. Lower panel: serotonin (5-HT) receptors involved in serotonergic signaling in the respective region.

after arrival to the glomerular layer but before the integration into the local circuit (Liang et al., 2016), functional properties of adult-born JGCs differ from those of resident cells. Thus, adult-born JGCs show lower spontaneous ongoing activity, higher odor sensitivity, greater responsiveness to a larger number of odorants, and increased structural plasticity. When adult-born JGCs mature (approximately at 7–8 weeks after birth), their spontaneous and odor-evoked activities and structural plasticity become more similar to those of resident juxtaglomerular cells (Fomin-Thunemann et al., 2020). However, many adult-born cells do not survive the maturation process and undergo apoptosis ~15–45 days after their birth. Interestingly, daily treatment with the selective 5-HT1A receptor agonist 8-hydroxy-2-(di-n-propylamino)tetralin significantly increased $BrdU^+$ cell survival in the dentate gyrus of the hippocampus while the same treatment decreased survival of $BrdU^+$ granule cells in the OB (Soumier et al., 2010). Taken together, these observations suggest that starting from their generation in the respective neurogenic niche and until their full maturation, the development of adult-born hippocampal and OB interneurons is controlled by the serotonergic inputs.

But do adult-born cells preserve their privileged serotonergic inputs beyond their maturation, i.e. at times, when their functional properties are supposed to align with those of surrounding resident cells? Our data obtained in mature adult-born JGCs (Fomin-Thunemann et al., 2020) suggest that this might be the case: after application of the nonselective 5-HT2/5-HT7 receptor antagonist methysergide onto the OB surface of awake mice, we observed a significant and selective decrease in the ongoing activity of mature (> 8 week-old) adult-born JGCs. Surprisingly, the same treatment did not influence resident cells. This suggests that despite their abundance in the glomerular layer, serotonergic fibers preferentially target adult-born cells. What could be the functional role of this privileged connection?

Serotonergic projections to the OB were shown to play a key role in selective filtering or attenuation of sensory inputs. Indeed, inhibition of serotonin receptors in general, and 5-HT2C receptors in particular enhanced odor-evoked responses in axons of olfactory sensory neurons projecting from the nose to OB glomeruli, whereas activation of 5-HT2C receptors inhibited these responses (Petzold et al., 2009). This effect was shown to be mediated through presynaptic $GABA_B$ receptors and was similar across all examined odorants and glomeruli, with stronger responses being affected to a greater extent than weaker responses. The authors suggested that this effect could be mediated by a subpopulation of GABAergic JGCs that express 5-HT2C receptors and respond to activation or inhibition of 5-HT2C receptors with a respective increase or decrease in odor-evoked Ca^{2+} signaling (Petzold et al., 2009). In addition to suppressing transmitter release from presynaptic terminals, GABAergic JGCs also contact and inhibit the postsynaptic targets of olfactory sensory neurons - mitral/tufted cells. Interestingly, not all JGCs analyzed by Petzold et al. (2009) were serotonin-responsive, suggesting that this property might be restricted to mature adult-born cells, as described above (Fomin-Thunemann et al., 2020). By controlling their ongoing spontaneous activity (Fomin-Thunemann et al. 2020), serotonergic inputs likely contribute to tonic presynaptic inhibition in the glomerular layer of the OB. Interestingly, serotonin-mediated reduction of sensory-evoked responses was also reported for visual and auditory systems (Petzold et al., 2009), suggesting that the ability of sensory gain control represents a general property of serotonergic inputs.

Serotonergic raphe neurons are active during awake resting states, including grooming and rhythmic movements, but not during attentive states of sensory acquisition or sleep (Jacobs and Fornal, 1991; Petzold et al., 2009). Thus, depending on the internal state of the animal and external - environmental - stimuli, serotonergic projections from the brainstem, targeting mature adult-born cells, might influence the strength of the perceived sensory stimulus. Serotonin-responsive adult-born JGCs therefore might serve as coincidence detectors between the internal state of the animal (e.g., arousal, attention, expectation) and sensory inputs from the environment. In this scenario, activation of serotonergic inputs would help to filter irrelevant information, adjust the gain of the system to odor detection/perception, and to maintain responses of mitral/tufted cells within a normal dynamic range. Moreover, the overall reduction of sensory-driven responses during wakefulness might help to reduce the system's noise and to select salient information important to learn or memorize. In the olfactory system, serotonergic signaling was shown to play an important role in the formation of short-term memory and associative conditioning (Fletcher and Chen, 2010). For instance, in neonatal rats, odor-preference learning was impaired when serotonergic inputs were depleted. In adult rats, reducing or blocking serotonergic signaling impeded discrimination of previously learned odorants as well as learning of new tasks (Fletcher and Chen, 2010).

In conclusion, serotonergic inputs support major steps of adult neurogenesis in both neurogenic niches of the mammalian brain, including cell proliferation, migration, and survival. Moreover, even after full integration of adult-born cells into the surrounding neural circuitry and maturation therein, serotonergic inputs convey unique functional properties to adult-born cells, enabling them to play a distinctive role in integrating environmental stimuli in a brain state-specific manner.

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