Serotonergic neurons project to virtually all regions of the central nervous system and are consequently involved in many critical physiological functions such as mood, sexual behavior, feeding, sleep/wake cycle, memory, cognition, blood pressure regulation, breathing, and reproductive success. Therefore, serotonin release and serotonergic neuronal activity have to be precisely controlled and modulated by interacting brain circuits to adapt to specific emotional and environmental states. We will review the current knowledge about G protein-coupled receptors and ion channels involved in the regulation of the serotonergic system, how their regulation is modulating the intrinsic activity of serotonergic neurons and its transmitter release and will discuss the latest methods for controlling the modulation of serotonin release and intracellular signaling in serotonergic neurons in vitro and in vivo.

Keywords: 5-HT system, GPCRs, auto-regulation, hetero-regulation, optogenetics

INTRODUCTION

The serotonergic system consists of a small number of neurons that are born in the ventral regions of the hindbrain (Deneris and Wyler, 2012). In the adult nervous system, serotonergic neurons [5-HT (5-hydroxytryptamine) neurons] are located in the nine raphe nuclei that are restricted to the basal plate of the midbrain, pons, and medulla (Dahlstrom and Fuxe, 1964). 5-HT neurons located in the rostral raphe nuclei, such as the dorsal raphe nucleus (DRN) and the median raphe nucleus (MRN), give rise to the majority of the serotonergic ascending fibers into the forebrain including cerebral cortex, limbic system, and basal ganglia (Jacobs and Azmitia, 1992). The activity of the serotonergic system is regulated via transmitter release from local interneurons and/or afferents to the raphe nuclei (hetero-regulation), via mechanisms arising from 5-HT neurons themselves (auto-regulation), and potentially via alterations in the extracellular milieu (e.g., increase in CO2; Pineyro and Blier, 1999; Richerson, 2004). In this review, we will discuss G protein-coupled receptors (GPCRs) and ion channels located at somatodendritic and presynaptic regions of 5-HT neurons in the DRN and MRN that contribute to the modulation of 5-HT neuronal activity and 5-HT release (Figure 1).

The DRN and MRN are the primary nuclei of 5-HT projections to forebrain and provide the neural substrate to communicate between global forebrain and other neuromodulatory systems by sending a wide range of 5-HT projections and receiving a wide variety of afferents (Jacobs and Azmitia, 1992). The DRN is located right beneath the posterior part of cerebellar aqueduct and contains about half of all 5-HT neurons in the central nervous system (CNS), which can be further divided into six regions: rostral, caudal, dorsomedial, ventromedial, interfascicular, and lateral parts. The MRN is located at the ventral expansion of the DRN or the midline of the pontine tegmentum where many 5-HT neurons are densely packed in the midline and some 5-HT neurons are scattered in the periphery. Within the DRN and MRN 5-HT neurons project to defined target area in brain (Adell et al., 2002; Lechin et al., 2006). For example, DRN 5-HT neurons innervate the prefrontal cortex, lateral septum, and ventral hippocampus, while MRN 5-HT neurons innervate the temporal cortex, medial septum, and dorsal hippocampus. Afferent projections to the raphe nuclei are diverse and include acetylcholine (ACh) from the lateral prefrontal neuronal activity have to be precisely controlled and modulated by interacting brain circuits to adapt to specific emotional and environmental states. We will review the current knowledge about G protein-coupled receptors and ion channels involved in the regulation of the serotonergic system, how their regulation is modulating the intrinsic activity of serotonergic neurons and its transmitter release and will discuss the latest methods for controlling the modulation of serotonin release and intracellular signaling in serotonergic neurons in vitro and in vivo.

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and physiological differences, it has been reported that subpopulations of 5-HT neurons have distinct implications in specific physiological function and behavior (Abrahms et al., 2004; Lechin et al., 2006; Hale and Lowry, 2010).

**AUTO-REGULATION**

The midbrain 5-HT neurons elicit spontaneous action potentials (APs), with a regular, slow firing pattern (1–5 APs/s; Aghajanian and Vandermaelen, 1982; Vandermaelen and Aghajanian, 1983). 5-HT released from 5-HT neurons acts either on the 5-HT neuron itself or on the target circuits. There are several ways how 5-HT neurons may receive 5-HT. First, dendrodendritic synapses releasing 5-HT have been described in raphe nuclei between 5-HT neurons. Second, recurrent axon collaterals have been suggested to back-propagate to the raphe nucleus itself to release 5-HT. Finally, 5-HT neurons between different raphe nuclei such as DRN and MRN communicate with each other via 5-HT (for review, see Adell et al., 2002; Harsing, 2006; Lechin et al., 2006). Indeed electrical stimulation in DRN slice preparations induces 5-HT receptor-mediated slow inhibitory postsynaptic potentials (IPSPs) in 5-HT neurons (Pan et al., 1989; Morikawa et al., 2000), demonstrating 5-HT release in the proximity of 5-HT neurons.

Once 5-HT is released, 5-HT receptors will be activated. Seven subgroups of 5-HT receptors encoding ionotropic as well as metabotropic receptors have been described (5-HT1–5-HT7), with 15 total variants identified to date (Barnes and Sharp, 1999; Hoyer et al., 2002; Koorevaar et al., 2002). The 5-HT GPCRs can be divided into three major subgroups depending on which G protein signaling pathway they activate. 5-HT1 receptors couple mainly to the Gi pathway; 5-HT2, 5-HT3, and 5-HT4 receptors couple to the Gq pathway; and 5-HT6 receptors activate the Gs/Al pathway. The 5-HT7 receptors are ligand-gated ion channels. 5-HT1A, 5-HT1B, and 5-HT1D receptors are found on somatodendritic and axonal region of 5-HT neurons (McDevitt and Vandenberg, 2000). All three receptors act as negative feedback effectors for 5-HT neuronal firing and 5-HT release (Andrade, 1998). Somatodendritically located 5-HT1A receptors down-regulate the firing rate of 5-HT neurons via activation of G protein-coupled inwardly rectifying potassium channels (GIRK) leading to membrane hyperpolarization, and reduction or complete block of AP firing (Colino and Halliwell, 1987; Sprouse and Aghajanian, 1987; Boeijinga and Boddeke, 1993; Morikawa et al., 2000). The functional consequence of Ca2+ channel inhibition is an increase in the firing rate due to reduction in the afterhyperpolarization, which may involve Ca2+ activated-K+ channel (Bayliss et al., 1997b). The physiological role of the differential effects of 5-HT1A receptors on the AP firing has not been addressed so far, but may involve input specificity due to 5-HT1A/GIRK and 5-HT1A/Ca2+ channel colocalization in specific subcellular domains and/or differences in the regulatory properties of heterogeneous 5-HT neurons within and among different raphe nuclei (Calizo et al., 2011).

The predominant 5-HT receptors at the presynaptic terminal are the 5-HT1B/D receptors. 5-HT1B/D receptors have been shown to inhibit 5-HT release from the axonal varicosities as demonstrated with electrophysiological experiments (Sprouse and Aghajanian, 1987; Ročičinica and Boddeke, 1993; Morikawa et al., 2000), probably due to inhibition of Ca2+ influx through voltage-gated Ca2+ channels such as P/Q-type and N-type Ca2+ channel (Kimura et al., 1995; Harvey et al., 1996). The 5-HT1B receptors have been shown to underlie presynaptic autoinhibition of 5-HT release in which 5-HT1A mediated slow IPSPs are reduced by previous released 5-HT activating presynaptic 5-HT1A receptors (Morikawa et al., 2000). In addition, 5-HT1B receptors have been suggested to up-regulate 5-HT reuptake by serotonin transporters (Xie et al., 2008; Hagan et al., 2012) and 5-HT synthesis by itself might be under the control of 5-HT1B (Hjorth et al., 1995). Thus, 5-HT1B autoreceptors may have the ability to control 5-HT release independently from the actual firing rate.

5-HT1F receptor mRNA has also been detected in the raphe nuclei (Bruinvels et al., 1994). Since 5-HT1F receptors have a high affinity for sumatriptan, a 5-HT1B/D agonist, and the sumatriptan-induced reduction in 5-HT release (monitored by voltammetry in brain slices) could not be blocked by 5-HT1B/D receptor antagonists, 5-HT1F had been suggested as a possible candidate of a serotoninergic autoreceptor in the MRN (Hopwood and Stamford, 2001).

While the expression and function of 5-HT1 receptors has been directly demonstrated in 5-HT neurons, involvement of other 5-HT receptors such as 5-HT1C, 5-HT1E, and 5-HT1F, –G is less clear and may differ among species, the developmental stage of the animal and 5-HT neuron subtypes.

5-HT2 receptors are functionally expressed in particular on GABAergic interneurons in the DRN, since activation of 5-HT2AD receptors increase fast inhibitory postsynaptic current (IPSC) frequency in 5-HT neurons and reduce 5-HT neuronal firing as electrophysiologically measured in brain slices (Liu et al., 2000; Leysen, 2004). 5-HT1/2 receptor mRNA and proteins have been identified in the DRN and embryonic 5-HT neurons (Wright et al., 1998; Cerretti et al., 2000; Wylie et al., 2010). Additionally, 5-HT2 receptors have been postulated to increase 5-HT1A-mediated responses in 5-HT neurons (Kidd et al., 1991). However, a direct modulatory effect of 5-HT2 in 5-HT neurons has not been demonstrated.

The 5-HT3 receptors have also been suggested to act as presynaptic autoreceptors in serotonergic nerve terminals. Although 5-HT3 receptors have been shown to enhance 5-HT release in various brain areas including the raphe nuclei as monitored by [3H]5-HT assays (Badgy et al., 1998), there is no direct immunohistochemical and electrophysiological evidence of the presence of 5-HT3 receptors in 5-HT neurons (van Hooff and Vijverberg, 2000).

For the G protein-coupled 5-HT4 receptors, mainly indirect evidence exists for an autoregulatory role of these GPCRs in 5-HT neurons.

5-HT4 receptors seem to be located somatodendritically and presynaptically. A presynaptic potentiating effect of 5-HT4 receptor on glutamate release, which can be counteracted by 5-HT1A receptor-mediated inhibitory action, has been described in...
FIGURE 1 | Intrinsic somatodendritic and presynaptic modulation of action potential (AP) firing and transmitter release in 5-HT neurons. (A) AP firing of 5-HT neurons is modulated by GPCRs and ion channels. AP firing is reduced (red arrows) via activation of GPCRs coupling to the Gi/o pathway or activation of inhibitory ligand-gated ion channels. Gi/o pathway activation can lead to the activation of GIRK channels, inhibition of voltage-gated Ca\(^{2+}\) channels or increase in GABA\(_{A}\) receptor currents. In addition, Gq/11 activation can lead to synthesis of endocannabinoids, which inhibit transmitter release onto 5-HT neurons. AP firing is increased (blue arrows) via activation of GPCRs coupling to the Gq/11 pathway or activation of excitatory ligand-gated ion channels. Gq/11 pathway activation can lead to the activation of non-selective cation channels or inhibition of K\(^{+}\) conductance. In addition, the activation of L-type Ca\(^{2+}\) channels via protein kinase C (PKC) can most likely increase membrane depolarization and transcription. (B) 5-HT release of 5-HT neurons is also modulated by GPCRs and ion channels. 5-HT release is reduced (red arrow) via activation of GPCRs coupling to the Gi/o pathway. Gi/o pathway activation leads to the inhibition of presynaptic Ca\(^{2+}\) channels, reduction in Ca\(^{2+}\) influx and therefore reduction in transmitter release. 5-HT release is increased (blue arrows) via activation of GPCRs coupling to the Gs pathway and via opening of excitatory ligand-gated ion channels.
hippocampal neurons (Kobayashi et al., 2008). Since neurotransmitter release of various transmitters including 5-HT is modulated by 5-HT1A agonists, a presynaptic localization of 5-HT1A receptors on 5-HT neurons seems possible (Meng et al., 2010).

While the function of 5-HT3 receptors in the CNS has not been thoroughly studied, two studies suggest a role of 5-HT3 receptors for modulating 5-HT neurons. First, 5-HT3A receptor mRNA, a receptor which is expressed in rodents but not in humans, is colocalized with the mRNA of 5-HT transporter in the DRN (Serrats et al., 2004). Second, block of 5-HT3A receptors in the DRN attenuates the 5-carboxamidotryptamine (5-CT; non-selective agonist) induced reduction of 5-HT neuronal firing but fail to affect 5-HT release measured using fast cyclic voltammetry in vitro (Thomas et al., 2006). The data suggest an autorceptor modulation of 5-HT neurons via 5-HT3A receptors.

5-HT4 and 5-HT7 receptor protein and mRNA have been detected in cells in the raphe nuclei including the DRN (Braat et al., 1993; To et al., 1995; Gustafson et al., 1996; Woolley et al., 2004; see also Gerard et al., 1997; Harrison et al., 1999), but a functional role as autoreceptors for modulating 5-HT neurons could not be demonstrated so far (Bourson et al., 1998; Roberts et al., 2001).

Thus, the auto-regulation of 5-HT neuronal firing is in particular regulated by 5-HT4 receptors via activation of the Gs pathway and opening K+ and closing Ca2+ conductance. At the presynaptic terminal, 5-HT1A receptor activation reduces 5-HT release most likely via Gs, protein-mediated inhibition of presynaptic Ca2+ channels. In addition, potentiation of 5-HT release by activating 5-HT4 receptors via the Gi pathway seems possible. Since other 5-HT4 receptor mRNA has been detected in 5-HT neurons, other autoregulatory mechanisms may exist in subgroups of 5-HT neurons or during different developmental stages of the serotonergic transmitter system. In particular, animal models for the selective activation of these GPCRs during development will further elucidate the modulatory role of other 5-HT receptors in the auto-regulation of 5-HT neuronal firing and 5-HT release.

**HETERO-REGULATION**

5-HT modulates various complex behaviors and therefore the serotonergic transmitter system receives feedback and feedforward information from other brain areas and networks involved in regulating the different behaviors (Adell et al., 2002; Lechin et al., 2006; Sharp et al., 2007). Thus, the hetero-regulation of the 5-HT neurons involves various transmitter systems.

Forty-nine different GPCRs belonging to all four GPCR subfamilies were identified in postmitotic embryonic 5-HT neurons using microarray expression profiling (Wylie et al., 2010). These GPCRs include adrenergic, calcitonin, cannabinoid, GABA, histamine, opioid, and serotonin receptors. For these transmitter systems, a postnatal modulatory role for 5-HT neurons has been addressed in various studies. In general, activation of GABAA receptor by selective agonists decreases 5-HT release (Bocquet et al., 1999a,b). The decrease of 5-HT release by GABAA receptors located within 5-HT neurons is most likely mediated via activation of GABAergic interneurons (Gallagher and Aghajanian, 1976; Williams et al., 1988; Bayliss et al., 1997a; Cornelisse et al., 2007). Within 5-HT neurons, GABAAR receptors are located extrasynaptically, suggesting that spillover of GABA during high activity of GABAergic neurons would modulate 5-HT neuronal activity within raphe nuclei (Sharp et al., 2007). On the other hand, there is little information about modulatory effects of metabotropic GluRs (mGluRs) in 5-HT neurons so far. Although administration of group II mGluR antagonist has been reported to increase 5-HT neuronal activity, an indirect effect on presynaptic excitatory neurons seems to be involved (Kawashima et al., 2000).

**CORELEASE OF GLUTAMATE OR GABA FROM 5-HT NEURONS**

Previous reports have suggested the possibility of glutamate release from 5-HT neurons based on the presence of vesicular glutamate transporter type 3 in a subset of 5-HT neurons (Gras et al., 2002; Amatullin et al., 2010). Using optogenetic techniques, the corelease of glutamate and 5-HT from serotonergic terminals could be demonstrated in a serotonergic projection from the MRN to hippocampal GABAergic interneurons (Varga et al., 2009). The serotonergic fibers make direct synaptic contacts to the GABAergic neurons and exert fast synaptic transmission mediated by ionotropic GluRs and 5-HT, receptors. In addition to the glutamate transporters, GABA and its synthesizing enzymes, glutamic acid decarboxylase (GAD) have also been reported in subsets of 5-HT neurons, suggesting the corelease of GABA and 5-HT
Very limited information is available for the expression and functional activity of D1-like receptors in the sleep-wake cycle. Dopamine increases the firing of 5-HT neurons (Bouthenet et al., 1987; Matsumoto et al., 1996; Mendlin et al., 2001) or by direct activation of D2 receptors expressed in 5-HT neurons (Yokoyama et al., 1994; Suzuki et al., 1998). Thus, 5-HT axonal projections have a potential to modulate the neuronal activity in target areas using at least three different transmitters, i.e., 5-HT, glutamate, and GABA. It is intriguing to speculate that the auto-regulation of 5-HT neurons itself might be modulated by corelease of glutamate and GABA.

**Acetylcholine**

The DRN also receives cholinergic input from the laterodorsal tegmental nucleus (Wang et al., 2000). Modulation of 5-HT neurons by ACh may involve nicotinic ACh receptors (nAChRs) and can increase 5-HT neuronal firing (Mihalcea et al., 2002) for example, via presynaptic modulation of glutamate release (Gardiano et al., 2012) or via opening of nAChRs expressed in 5-HT neurons (Galindo-Charlez et al., 2008; Chang et al., 2011). Very limited information is available for the expression and functional activity of muscarinic ACh receptors (mAChRs) in 5-HT neurons. mAChRs-M1 receptors (Go11) might be expressed on serotoninergic projections into the hippocampus (Rouse and Levey, 1996) and application of mAChR antagonist, atropine into the DRN inhibits 5-HT neuronal firing in DRN slice preparation (Rouse and Levey, 1996). The direct effect of mAChRs in 5-HT neurons is essential.

**Dopamine**

The 5-HT neurons of the DRN reciprocally interact with the dopaminergic mesencephalic transmitter system involving dopamine receptors. D1-like receptors (D1 and D5) couple to the dopaminergic mesencephalic transmitter system involving dopamine receptors. D1-like receptors (D1 and D5) couple to G蛋白偶联型的 5-HT neurons (Vandermaelen and Aghajanian, 1983) and may involve the suppression of a 4-aminopyridine sensitive K+ conductance (Joh Aghajanian, 1985). In vivo experiments suggest that D1 receptors are tonically activated by endogenous NA (Adell et al., 1999; Pudovkina et al., 2003). In contrast, 5-HT release detected by voltammetry or [3H]5-HT assay in the DRN slice preparation is inhibited by NA, an effect which has been attributed to D2 adrenoceptors (presumably D2 adrenoceptor subtype) and also perhaps indirectly to D1 adrenoceptors (Frankhuijzen et al., 1988; Hopwood and Stamford, 2001). Since D2 receptors couple to the Goi pathway, 5-HT release and 5-HT neuronal firing could be reduced via D2 adrenoceptors located at the soma or presynaptic terminal of 5-HT neurons itself (Hopwood and Stamford, 2001), or via inhibition of NA release at noradrenergic synaptic terminals lowering the effective NA concentration for 5-HT neurons in the DRN (Lakoski and Aghajanian, 1983).

**Histamine**

There are four histamine receptors (H1-4), which couple to different G protein pathways, i.e., H1 (Go11), H2 (Gq), H3, and H4 (Gq). Early studies suggested that histamine reduces the firing of 3-HT neurons in the DRN (Lakoski and Aghajanian, 1983) via H2 receptors (Lakoski et al., 1984). Since H2 couples to the Go11 pathway, the results suggest that H2 receptors are localized on GABAergic terminals. Later findings showed that histamine increased 5-HT neuronal firing in the DRN via activation of H1 receptors and the opening of a non-selective cation conductance through Go11 signaling pathways (Barbara et al., 2002; Brown et al., 2002). Expression profiling in mouse embryos suggested the expression of H3 receptors in 5-HT neurons, which is consistent with high mRNA levels in the DRN (Lawenborg et al., 1999; Drutel et al., 2001; Pilot et al., 2002). However, the low binding
of a H3 receptor selective radioligand in the DRN suggests that H3 receptors are mainly functional at the presynaptic terminal of 5-HT projections (Vilat et al., 2002). Indeed increasing levels of histamine decrease 5-HT release detected by in vivo electrochemical technique (Hashemi et al., 2011).

**E N D O C A N N A B I N O I D S**

The cannabinoid receptor family consists of two subtypes, CB1, and CB2. Modulation of neuronal activity is mainly exerted via CB1, which couples to the Gq/11 pathway, and is localized in particular at presynaptic terminals, where they inhibit presynaptic Ca2+ influx and reduce transmitter release via an endocannabinoid (eCB)-mediated retrograde signaling (Masujiama et al., 2001). CB1 receptors are expressed in serotonergic fibers (Haring et al., 2007; Ferreira et al., 2012) and their mRNA is found in vivo (Darmani et al., 2003; Tzavara et al., 2009). Studies in CB1 knock-out animals and chronic activation of CB1 receptors in vivo suggest that CB1 may regulate the function and expression of 5-HT1A receptors (Aso et al., 2009; Morantza et al., 2009; Zavitsanou et al., 2010). Interestingly, 5-HT neurons itself synthesize eCBs in an activity-dependent manner (Haj-Dahmane and Shen, 2009, 2011). eCB release from 5-HT neurons can be induced by orexin-B leading to the activation of orexin (OX) receptors via the Gq/11 pathway (Liu et al., 2002b; Haj-Dahmane and Shen, 2005). It has been therefore speculated that the activity-dependent activation of the Gq/11 pathway in general may lead to the production of eCBs in 5-HT neurons (Haj-Dahmane and Shen, 2011). Within the DRN eCBs mainly act on glutamatergic terminals and probably also on GABAergic terminals (Liu et al., 2002b; Haj-Dahmane and Shen, 2009; Mendiguren and Pineda, 2009; Tao and Ma, 2012), leading to a reduction in glutamate and GABA release onto 5-HT neurons and therefore changes the activity of the 5-HT neurons itself.

**FRIZZLED RECEPTORS**

Four frizzled receptors (FZD1–3 and SMO) have been detected in postmitotic embryonic 5-HT neurons (Wylie et al., 2010). These receptors mainly couple to the Wnt signaling cascade and are most likely involved in the development and maturation of 5-HT neurons (Simon et al., 2005; Song et al., 2012). However, the role of frizzled receptors in 5-HT neurons remains to be determined.

**NEUROPEPTIDES**

Dr. Hökfelt’s laboratory demonstrated that various peptide transmitters are expressed in the DRN with species-specific differences early in development (Wylie et al., 2010). 5-HT release in projection areas from the DRN is reduced by activation of CB1, as monitored by microdialysis (Egashira et al., 2002) and c[3H]5-HT assay (Nakazi et al., 2000; Egashira et al., 2002), and increased by inhibition of CB1 in vivo and in vitro (Darmani et al., 2003; Tzavara et al., 2003; Aso et al., 2009). Studies in CB1 knock-out animals and chronic activation of CB1 receptors in vivo suggest that CB1 may regulate the function and expression of 5-HT1A receptors (Aso et al., 2009; Morantza et al., 2009; Zavitsanou et al., 2010).

Calcitonin receptor (CalcR) mRNA has been localized in 5-HT neurons (Nakamoto et al., 2000), which is in agreement with the expression profiling studies of postmitotic embryonic 5-HT neurons (Wylie et al., 2010). The CalcR couples to the Gi/o pathway (Hay et al., 2005) and Gq/11 pathway (Olfertmanns et al., 1996). Since high levels of amylin binding sites are detected in the DRN (Sixton et al., 1994) and mRNA for CGRP has been localized in 5-HT positive axon terminals in monkeys (Arvidsson et al., 1990), it is most likely that CalcR assembles with receptor-activating-modifying proteins (RAMPs) in 5-HT neurons to respond to the various peptide transmitters (i.e., CGRP, adrenomedullin, and amylin; Tilakaratne et al., 2000). A direct function of CalcR in 5-HT neurons has not yet been demonstrated. However, injection of CGRP into rats induces anxiety-like behaviors and increases c-Fos expression in the DRN (Sink et al., 2011).

**CHEMOKINE RECEPTORS**

Two subtypes of the 18 identified chemokine receptors have been detected in microarray analyses from embryonic 5-HT neurons, i.e., Duffy antigen/chemokine (C-X-C motif) receptor 4 (CXCR4; Wylie et al., 2010). CXCR4 is expressed in the majority of 5-HT neuron outer membranes in the DRN (Heinisch and Kirby, 2010). So far only an indirect action of CXCR4 for modulation of the CX3CR1 ligands and antagonists modulate GABA and glutamate release onto 5-HT neurons (Heinisch and Kirby, 2010), which is in agreement with the described Gqα protein-mediated inhibition of Ca2+ channels via CXCR4 (Oh et al., 2002). In addition, CXCR1 is also expressed in 5-HT neurons in the DRN and MBN (Heinisch and Kirby, 2009). Here the CXCR1 specific ligand, fractalkine/CX3C1L1 increased evoked IPSC amplitude on 5-HT neurons (Heinisch and Kirby, 2009), an effect which is mostly mediated postsynaptically and not presynaptically. The effect is surprising, since CXCR1 has been described to couple to the Gq/11 pathway (Oh et al., 2002), which would inhibit synaptic transmitter release and induce paired pulse facilitation (PPF) if activated on GABAAergic terminals. Therefore, the CXCR1 could increase/modulate GABAA receptor trafficking and GABAA receptor signaling.
receptor currents in 5-HT neurons via activation of CXCR1. A signaling function for Duffy antigen remains to be determined.

**CHOLECYSTOKININ**

The expression of CCK receptors in 5-HT neurons in the DRN has also been suggested. Application of CCK increases 5-HT neuronal firing, which is blocked by the CCK1 antagonist L-364,718 (Boden et al., 1991). In addition, 5-HT release measured as outflow of [3H]5-HT in cortical slices is increased by CCK-4, which involves CCK2 receptors (Smisalci et al., 2001). Both CCK1 and CCK2 receptors mainly couple to the Gq/11 and G12 pathway (de Wied et al., 1993; Lee et al., 1993; Ulrich et al., 1993).

**CORTICOTROPIN-RELEASING FACTOR**

Two CRF (CRF1 and CRF2) receptor subtypes have been described in brain and both seem to be localized in GABAergic neurons in the DRN as well as in 5-HT and non-5-HT neurons with differential subcellular localizations (for review, see Valentino et al., 2010). CRF2 and CRF1 couple to the Gq pathway (Chang et al., 1993; Ferri et al., 1996; Vita et al., 1993; Lovenberg et al., 1995; Liaw et al., 1996) and also the Gq/11 pathway in heterologous expression systems (Dussaule et al., 2004), leading to the assumption that stimulation of CRF1 or CRF2 will increase neuronal firing. Indeed, activation of CRF1 on GABAergic neurons increases GABA release onto 5-HT neurons, while activation of CRF2 elicits an inward current in 5-HT neurons (Kirby et al., 2008). Based on the differential localization of the CRF receptors within the DRN and its receptor type-specific action on 5-HT neurons, it has been suggested that at low concentrations of CRF, 5-HT neuronal activity is decreased, while at high concentrations, 5-HT neuronal activity is increased (Kirby et al., 2008; Valentino et al., 2010).

**GALANIN**

The neuropeptide galanin activates three types of galanin receptors (GalR1, GalR2, and GalR3) that are highly expressed in the DRN (Melander et al., 1988; Larm et al., 2003; Li et al., 2005; Sharkey et al., 2008). Moreover, GalR2 expression has also been described in 5-HT neurons from rats but not in mice (Xu et al., 1998; Larm et al., 2003). GalR activation in the DRN causes a K+ conductance-mediated hyperpolarization in rat brain slices (Xu et al., 1998), most likely via GalR3-mediated GIRK channels (Swanson et al., 2005). These effects are in agreement with in vivo microdialysis studies showing that injection of galanin into the DRN reduces 5-HT release via GalR activation in the hippocampus (Kehr et al., 2002). In contrast to the inhibitory action of galanin in 5-HT neuronal activity, a reduction in inhibitory input onto 5-HT neurons has also been described (Sharkey et al., 2008). Here, the pan-GalR1,2 agonist reduced GABA-mediated fast synaptic transmission accompanied by increase of PPF, suggesting that GalRs are expressed on GABAergic terminals and inhibit presynaptic Ca2+ channels via the Gq/11 pathway. On the other hand, GalR2 agonist, galalin (2-11) reduced IPSP amplitude but did not cause PPF, suggesting a post synaptic action (Brand AB et al., 2000; Sharkey et al., 2008). Additionally, galalin (2-11) was demonstrated to increase 5-HT release in hippocampal tissue by immunofluorescence and high-performance liquid chromatography (HPLC) measurement (Mazurati et al., 2005). Therefore GalR2 receptors may activate 5-HT neurons via reduction in GABAergic input onto 5-HT neurons and/or via Gq/11-mediated increase in 5-HT neuronal firing. Galanin also modulates 5-HT1A autoreceptor responses in vivo. A possible mechanism of this modulation could be the heterodimerization of GalR with 5-HT1A, which has been observed in heterologous expression systems (for review, see Kuteeva et al., 2008; Borroto-Escuela et al., 2010).

**HYPNOTIC-OREXIN**

The two hypocretin/orxin (OX1 and OX2) receptors are expressed in tryptophan hydroxylase-positive neurons in the DRN (Brown et al., 2002). Their intracellular signaling targets are rather complex involving activation of G3a, G3z, Gq, and other G proteins (Scammell and Winrow, 2010). Orexin positive fibers project onto GABAergic as well as 5-HT neurons in the DRN (Pepron et al., 1998). Application of the neuropeptides orexin-A and orexin-B causes a Na+/K+ non-selective cation current in 5-HT neurons (Brown et al., 2002; Liu et al., 2002b; Kohlmeier et al., 2008), suggesting that activation of OX1 and OX2 leads to the increase of 5-HT neuronal firing. The neuropeptides also induce GABA release onto 5-HT neurons at higher peptide concentrations (Liu et al., 2002b). In addition, orexin increases the somatic L-type Ca2+ current in 5-HT neurons in a protein kinase C-dependent manner (Kohlmeier et al., 2008). It has therefore been suggested that modulation of Ca2+ transients by orexin may be involved in the transcriptional regulation of long-term processes (Kohlmeier et al., 2008).

**OPIOIDS**

Rape nuclei receive dynorphinergic, enkephalinergic, and δ-endorphinergic innervation (Adell et al., 2002). These transmitter systems activate μ, δ, and κ opioid receptors, which primarily couple to the Gq/11 pathway. Injection of morphine into the DRN causes an increase in 5-HT release detected in forebrain microdialysis (Tao and Auerbach, 1994). The increase in 5-HT release is most likely mediated via G3a protein-mediated inhibition of GABAergic interneurons in the DRN, involving μ and κ opioid receptors located on GABAergic neurons (Joras and Aghajanian, 1997). The modulation of 5-HT release in the DRN by δ and κ opioid receptors has also been described (Tao and Auerbach, 2002). Activation of δ receptors increased, while activation of κ receptors decreased 5-HT release measured with in vivo microdialysis. The κ receptors effects do not involve the modulation of GABAergic or glutamatergic inputs in the DRN (Tao and Auerbach, 2002), suggesting that κ receptors are expressed in 5-HT neurons. Likewise, opioid receptor-likers (Oprl1) are most likely located and expressed in 5-HT neurons as follows. Oprl1 or nociceptin (NOP) receptors belong to the opioid receptor family but are activated by NOP (orphanin FQ), a neuropeptide derived from proenkephalin protein. High levels of NOP receptor binding sites have been detected in the DRN (Florio et al., 2000) and Oprl1 receptor expression could be detected in embryonic 5-HT neurons (Wylie et al., 2010). NOP/orphanin FQ inhibits 5-HT release in the DRN via Oprl1 (Tao et al., 2005), suggesting a functional role of Oprl1 in 5-HT neurons early in development and in the adult brain.
SUBSTANCE P

Substance P belongs to the tachykinin family and has a high affinity for the three different neurokinin receptors (NK1, NK2, NK3), in particular to NK1 (Hubbell et al., 2001). These GPCRs couple mainly to the G\textsubscript{\alpha}11 pathway (Stratowa et al., 1995), but G\textsubscript{i} pathway activation has also been reported for NK2 in cell culture systems (Martini et al., 2002). Various histological studies have revealed extensive expression of NK1 receptors in the DRN (Maeno et al., 1993; Safroy et al., 1994; Vigna et al., 1994; Chauara and Parent, 1998; Sergeres et al., 1999, Froger et al., 2001). Most studies suggest that NK1 receptors are not localized on 5-HT neurons (Froger et al., 2001; Santarelli et al., 2001), while others revealed NK1 receptor expression in a subpopulation of 5-HT neurons (Santarelli et al., 2001; Lacoste et al., 2006, 2009).

Interestingly, NK1 receptors are found in the cytoplasm of the 5-HT neurons and in dendritic membranes of GABAergic neurons. After administration of NK1 antagonist or deafferentation of substance P releasing projections, the density of membrane bound NK1 receptors is increased in the soma-dendritic region of 5-HT neurons, suggesting that membrane trafficking of NK1 receptors may be regulated by Substance P input. This mechanism may contribute to the modulation of 5-HT neuronal firing under certain physiological conditions (Lacoste et al., 2009). In addition, controversial results exist for the effect of NK1 on 5-HT release and firing of 5-HT neurons. Inhibition of NK1 in the DRN using antagonists or knock-out strategies leads to an increase in firing activity of 5-HT neurons in vivo (Haddjeri and Blier, 2001; Santarelli et al., 2001). In contrast, activation of NK1 and NK3 increases spontaneous excitatory postsynaptic currents (EPSCs) in DRN 5-HT neurons resulting in an increased firing of the 5-HT neurons as observed in brain slice recording (Liu et al., 2002a). These effects could be blocked by NK1 and NK3 antagonists (Liu et al., 2002a). Also, activation of NK1 via intrathecal injection of substance P in the DRN increases 5-HT release within the DRN, but decreases 5-HT release in frontal cortex as measured with in vivo microdialysis (Guandil et al., 2007). These effects and also the described increase in 5-HT firing in NK1 knock-out mice involve changes in 5-HT\textsubscript{1A} autoreceptor levels, suggesting at least a functional coupling between NK1 and 5-HT\textsubscript{1A} receptors. Further investigations to verify these interactions in 5-HT neurons are required.

In summary, the various heteroreceptors integrate incoming information via two main pathways, i.e., G\textsubscript{\alpha}o and G\textsubscript{\alpha}11, leading to inhibition or activation of 5-HT neuronal firing and 5-HT release, respectively. Besides the “classical” G\textsubscript{\alpha}o protein-mediated, membrane-delimited modulation of GIRQ and presynaptic Ca\textsuperscript{2+} channels, other ion channel targets have been identified in 5-HT neurons. For example, two-pore-domain K\textsuperscript{+} channels (TWIK-related acid-sensitive K-1 (TASK-1) and TASK-3) have been described in dorsal and caudal raphe 5-HT neurons (Wadhurn et al., 2002). TASK channels are inhibited by GPCRs coupling to the G\textsubscript{\alpha}11 pathway most likely in a membrane-delimited manner involving the direct binding of Gaq subunits (Chen et al., 2006). The existence of voltage sensitive but not ATP dependent K\textsuperscript{+} channels in DRN neurons including 5-HT neurons have been proposed based on drug application studies (Harsing, 2008).

In addition, TRP channels have been described to be modulated by D\textsubscript{2} like receptors (Aman et al., 2007). According to the microarray expression profiling studies, various ion channel targets of GPCRs are expressed in embryonic 5-HT neurons including TRP (Trpm4 and Trpm7), two-pore channels (TPCN1), cyclic nucleotide gate channels (Hcn3), and KCNQ (Kcnq2, Wylie et al., 2010). Therefore, more detailed studies have to be performed to determine the role of other ion channel targets and in particular long-term effects of GPCR modulation for the serotonergic system.

INTEGRATION AND SIGNAL PROCESSING OF MODULATORY INFORMATION BY SEROTONERGIC NEURONS: WHY SO MANY GPCRs?

The serotonergic transmitter system modulates many physiological functions such as mood, sexual behavior, feeding, sleep/wake cycle, memory, cognition, blood pressure regulation, breathing, and reproductive success (Mooney et al., 1998; Abrams et al., 2004; Lechun et al., 2008; Lefebvre et al., 2008; McDevitt and Neumaier, 2011). Because of the complexity and variety of the different behaviors modulated by serotonin, it is expected that modulatory signals from other brain areas including sensory information is integrated by GPCR signals in nuclei containing 5-HT neurons using a high diversity of GPCRs. While GABA and glutamatergic input into the raphe nuclei will adjust 5-HT neurons to the current inhibitory/excitatory state of the brain, other transmitter systems will inform 5-HT neurons more directly about the serotonin-associated behavior. For example, dopamine is involved in reward-driven learning. ACh modulates arousal and reward; NA and CRF are involved in stress responses; histamine is involved in sleep regulation and sexual function; bombesin and CCK regulate eating behavior; eCBs modulate memory, appetite, stress, social behavior, anxiety, and sleep; galanin has been implicated in the regulation of sleep–wake cycle, cognition, emotion, and blood pressure; hypocretin–orexin modulate arousal, wakefulness, and appetite, and opioids and substance P are involved in pain perception and mood (White and Rumschild, 1988; Woolf et al., 1996; Greenough et al., 1998; Bear et al., 2001; Merali et al., 2006; Monti, 2010; Haji-Dahmane and Shen, 2011). Since all different behavioral responses can be integrated in nuclei containing 5-HT neurons, regulation of serotonin release will affect similar behaviors as stated above. Thus there is a tight integration and signaling exchange between the different transmitter systems to precisely modulate behavioral output. Consequently, long-term changes in serotonin release can involve changes in the auto-regulation involving 5-HT receptor or hetero-regulation involving the above mentioned GPCRs and can cause neuropsychiatric disorders, most notably depression, anxiety, schizophrenia, and dementia (Lucki, 1998; Davidson et al., 2005; Mann et al., 2011; Nelson and Chauvegat, 2001).

The modulation of the different behaviors is even more complex since other GPCRs, such as orphan GPCRs, with so far unknown function are also expressed in 5-HT neurons. Therefore, new strategies and techniques have to be applied and developed to understand complex behaviors related to the serotonergic system.
NEW APPROACHES TO CONTROL AND UNDERSTAND SEROTONERGIC G PROTEIN-COUPLED RECEPTOR SIGNALING PATHWAYS

Recently, several new approaches have been developed to manipulate the activity of 5-HT neurons in a cell-type-specific manner. These have included chemical and optogenetic techniques, as well as the use of genetically modified reporter genes.

For the investigation of the modulation and function of neuronal circuits in general, and for the serotonergic system in particular, chemical and optogenetic techniques have been developed in recent years (Herlitze and Landmesser, 2007; Masseck et al., 2010). For control of neuronal activity in various neuronal circuits including the 5-HT system, light-gated non-selective cation channel, CbH2 has been used and allows for the dissection of 5-HT-mediated behavioral effects in different raphe nuclei (Li et al., 2005; Varga et al., 2009; Zhao et al., 2011; Madsen et al., 2012; see also Kim et al., 2009). For the investigation of GPCR signals, various chemically and light-activated GPCRs have been developed (Masseck et al., 2010). For example, vertebrate rhodopsin (vRh) has been used to regulate Ca2+ signaling pathways in neurons by light (Li et al., 2005). Exogenously expressed vRh inhibits neuronal firing and neurotransmitter release in vitro and in vivo.

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Maejima et al. Modulation of 5-HT neurons

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May 2013 | Volume 7 | Article 40 | 15

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