serotonin in learning and plasticity

pt. 1 immediate action
Figure 5. Prototypical Glutamatergic Synapse Modulated by Serotonergic Input

The model character of this hypothetical synapse allows depiction of multiple receptors and their postreceptor signal transduction, transsynaptic interactions of adhesion molecules, and related intracellular signaling pathways regulating synaptic plasticity in a single schematic representation. For simplification purposes only a fraction of 5-HT receptor subtypes is depicted. Somatodendritic (5-HT1A) and terminal autoreceptors (5-HT1B) induce hyperpolarization that decreases the firing rate of 5-HT neurons. 5-HT2A and 5-HT2C basically activate phospholipase C (PLC) via the Gq protein but also impact a wide range of distinct signal transduction pathways by associating with multiple GPCR interacting proteins. The 5-HT2C stimulates the phosphoinositol second messenger cascade which, in turn, stimulates the activation of protein kinase C (PKC) and opens L-type Ca\(^{2+}\) channels. The protein phosphatase and tensin homolog (PTEN) binds to the 5-HT2C receptor which also interacts with several proteins, such as postsynaptic density (PSD) proteins containing PSD-95-disc large-zonula occludens (PDZ) domains. Association of 5-HT2C receptors with PDZ domain-containing proteins affects both receptor desensitization and internalization, depending on the type of the PDZ protein associated with the receptor. Neurexins (NRXNs) and their postsynaptic binding partners neuroligins (NLGNs), leucine-rich repeat transmembrane proteins (e.g., LRRTMs, FLRTs) and adhesion G protein-coupled receptors (adhesion-GPCR; e.g., latrophilins, LPHNs). Other synaptic adhesion proteins are members of the immunoglobulin superfamily (e.g., neural cell adhesion molecules, NCAMs) or cadherin family (e.g., CDH9, atypical CDH13). NRXNs interact with the scaffolding molecule CASK and NLGNs interact with the scaffolding molecule PSD-95 or SAP-97, which binds NMDA and AMPA receptors (NMDAR and AMPAR) via their PDZ domain. Alternatively spliced NRXNs bind the postsynaptic adhesion molecule LRRTM2, which can recruit NMDARs and AMPARs. NCAMs interact with the fibroblast growth factor receptor (FGFR) signaling (PI3K, ERK, AKT, GSK3, mTOR) pathway, which is also activated by CDHs. Several intracellular signaling pathways may be activated by LPHNs including Ca\(^{2+}\) dependent and -independent mechanisms. Moreover, LPHNs' C-terminal region interacts with proteins of the SHANK family. SHANK proteins are synaptic multidomain PSD scaffolding proteins binding to HOMER proteins, another group of postsynaptic density scaffolding proteins, which, in turn, are able to interact with mGLUR5. SHANK and HOMER proteins cross-link mGLURs with LPHNs. 5-HT1A activation decreases NMDA receptor-mediated currents in PFC pyramidal neurons through reduction of ERK1/2 activity, which leads to a decrease in microtubule-associated protein-2 (MAP2) phosphorylation, MAP2-microtubule interaction and microtubules stability involved in clustering the NMDA 2B subunit. In contrast, 5-HT2A/2C activation increases NMDA receptor-mediated currents by activating the ERK1/2 pathway, thus counteracting the effects of 5-HT1A activation in decreasing NMDA receptor-mediated currents. Metabotropic glutamate receptors (e.g., mGluR5, mGluR7) stimulate protein kinase A (PKA) and PKC pathways. mGluR5 not only interacts with signaling of 5-HT receptors but also with NMDA receptors resulting in reciprocal and agonist-independent inhibition of the two receptors. P11 and GSK3 may directly interact with 5-HT1B.
serotonin or 5-hydroxytryptamine (5-HT) derived from tryptophan

L-Tryptophan

O₂ Tetrahydrobioplerine

Hydroxytetrahydrobioplerine

5-Hydroxy-L-tryptophan (5-HTP)

Pyridoxal phosphate

5-Hydroxytryptophan decarboxylase
Aromatic L-amino acid decarboxylase

Serotonin (5-HT)

O₂ H₂O

Monoamine oxidase (MAO), Aldehyde dehydrogenase

5-Hydroxyindoleacetic acid (5-HIAA)
serotoninergic centers in the brain stem

raphe nuclei:
B1  raphe pallidus
B2  raphe obscurus
B3  raphe magnus
B5  raphe pontis
B6/B8 Nu. centralis sup.
B7  dorsal nu. raphe

Duvernoy 2009
5HT3 is an ionotropic receptor
all other 5HT receptors
are G-protein linked

5HTT or SERT
presynaptic
transporter (reuptake)

intracellular:
Vesicular
MonoAmine
Transporters

both ionpump coupled

receptors

Stahl 2008
5-HT function modifying compounds or toxins causing long-term expression changes persisting into adulthood. Moreover, genetic variation in key players of 5-HT system development has been shown to affect the 5-HT's neuromodulatory capacity with consequences for the cognition-emotion continuum (Gross and Hen, 2004; Pessoa, 2008).

Multiplicity of Signaling Pathways

Serotonergic input into neural networks implicated in sensory processing, cognitive control, emotion regulation, autonomic responses, and motor action is composed of two distinct 5-HT systems differing in their topographic organization, electrophysiological signature, morphology, and sensitivity to neurotoxins (Figure 2). There are at least fourteen structurally and pharmacologically divergent 5-HT receptors (Barnes and Sharp, 1999; Millan et al., 2008). Beyond isoform diversity, alternative splicing of some subtypes (e.g., 5-HT4) and RNA editing of the 5-HT2C receptor add to the diversity of the 5-HT receptor family. It continues to be a daunting task to dissect the physiological impact of individual receptors, design selective ligands to target specific subtypes, and determine potential therapeutic value of novel compounds. Molecular characterization of 5-HT receptor subtypes, functional mapping of transcriptional control regions, and the modeling of 5-HT receptor gene function in genetically modified mice has yielded valuable information regarding respective roles of 5-HT receptors and other components of serotonergic signaling pathways in brain development, synaptic plasticity, and behavior.

The well-characterized 5-HT1A subtype is a G protein-coupled receptor (GCPR) that operates both pre- and postsynaptically (Figure 2). Somatodendritic 5-HT1A autoreceptors are predominantly located on the soma and dendrites of neurons in the raphe complex and its activation by 5-HT or 5-HT1A agonists induces hyperpolarization, decreases the firing rate of $DR$.

Lesch & Waider 2012
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Serotonergic input into neural networks implicated in sensory processing, cognitive control, emotion regulation, autonomic responses, and motor action is composed of two distinct 5-HT systems differing in their topographic organization, electrophysiological signature, morphology, and sensitivity to neurotoxins and psychoactive compounds (Figure 2). There are at least fourteen structurally and pharmacologically divergent 5-HT receptors (Barnes and Sharp, 1999; Millan et al., 2008). Beyond isoform diversity, alternative splicing of some subtypes (e.g., 5-HT4) and RNA editing of the 5-HT2C receptor add to the diversity of the 5-HT receptor family. It continues to be a daunting task to dissect the physiological impact of individual receptors, design selective ligands to target specific subtypes, and determine potential therapeutic value of novel compounds. Molecular characterization of 5-HT receptor subtypes, functional mapping of transcriptional control regions, and the modeling of 5-HT receptor gene function in genetically modified mice has yielded valuable information regarding respective roles of 5-HT receptors and other components of serotonergic signaling pathways in brain development, synaptic plasticity, and behavior.

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Figure 2. Modulation of Glutamate- and GABA-Mediated Transmission by 5-HT in the Cortex, Striatum, Hippocampus, and Amygdala

For example, excitatory transmission within hippocampal areas CA1–3 is largely based on three glutamatergic pathways: the perforant path formed by axons of layer II stellate cells in the entorhinal cortex, the mossy fiber axons originating from the dentate gyrus granule cells, and the recurrent axon collaterals of CA1–3 pyramidal cells. The synaptic communication of each of these pathways is modulated by 5-HT receptors that fine-tune synaptic signal by affecting both the timing and strength of the connection. 5-HT1B receptors, located on axon terminals from pyramidal neurons and on their recurrent collaterals, inhibit glutamate release to neighboring pyramidal neurons and to local interneurons. The release of GABA from CA1 inhibitory interneurons is stimulated by 5-HT2 and by 5-HT3 receptors and inhibited by 5-HT1A receptors. 5-HT and GABAB receptors, respectively, increase and decrease T-type Ca2+ current on interneurons from stratum lacunosum moleculare. In the dentate gyrus, 5-HT3 receptors stimulate GABA release from interneurons. In CA3 pyramidal neurons, 5-HT inhibits GABAB receptor-mediated currents acting both pre- and postsynaptically; 5-HT and GABAB receptors cooperate in increasing a hyperpolarizing outward potassium current.

Several 5-HT receptors are also expressed by cells of dorsal striatum including the medium-sized spiny neurons (MSN), the tonically active cholinergic interneurons (TAN). In other brain regions distinct 5-HT receptors are required for different forms of pre- and postsynaptic long-term plasticity and also have been implicated in regulating short-term plasticity. Presynaptically expressed 5-HT receptors affect the timing of action potentials elicited in the postsynaptic target and they are be distributed in a target-specific manner, such that synaptic input from one presynaptic neuron can be modulated by different receptors at each of its postsynaptic targets. 5-HT signaling specifies a mechanism for synaptic specialization of glutamatergic and GABAergic transmission and thus contributes to the strength and timing of network activity within pyramidal cells, other principle neurons and interneurons.
receptors

classical 5HT1A in hippocampus mediates neuronal inhibition by
binding to specific ion channels

downregulated by chronic stress

variation in genes associated with negative emotionality, anxio-depressive disease spectrum
receptors

postsynaptic 5HT1A in hippocampus mediates neuronal inhibition by binding to specific ion channels
downregulated by chronic stress

variation in genes associated with negative emotionality, anxio-depressive disease spectrum

5HT2A/C can bind to a variety of GPRCs ⇒ impact on many different pathways

mainly activating PLC

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Serotonergic input into neural networks implicated in sensory processing, cognitive control, emotion regulation, autonomic systems differing in their topographic organization, electrophysiological signature, morphology, and sensitivity to neurotoxins

Multiplicity of Signaling Pathways

5-HT projections
Basket axon system (M fibers)
Thin, varicose axon system (D fibers)
Dorsal hippocampus
CA3
CA1
Midbrain
DR
Pyramidal neuron
GABAergic neurons
PV
Non-PV

PD

Noradrenergic system

Figure 2

Neuron

Barnes and Sharp, 1999
Millan et al., 2008

Gross

Pessoa, 2008

BLA
LA

DR

5-HT projections

5-HT1A
5-HT1B
5-HT2A
5-HT2C
5-HT3
5-HT4

Prefrontal cortex

Dorsal striatum

Amygdala

CA1
CA3

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Several 5-HT receptors are also expressed by cells of dorsal striatum including the medium-sized spiny neurons (MSN), the tonically active cholinergic interneurons of the substantia nigra, and the interneurons of the ventral tegmental area (VTA) and nucleus accumbens (NAc). Postsynaptic 5-HT1A receptors mediate neuronal inhibition by binding to specific ion channels and are downregulated by chronic stress.

The well-characterized 5-HT1A subtype is a G protein-coupled receptor (GCPR) that operates both pre- and postsynaptic to the activated receptor. As a GCPR, the 5-HT1A receptor couples to a heterotrimeric G protein and activates PLC, which in turn stimulates IP3 and DAG production, leading to the mobilization of intracellular calcium stores and activation of PKC. PLC is one of the best-studied downstream signaling molecules in G protein-coupled receptors (GPCRs), which have been shown to impact many different pathways.

5-HT1A autoreceptors act to fine-tune 5-HT release from raphe neurons, and the local processes and cells expressing 5-HT1A receptors include serotonergic neurons themselves, as well as neurons and astrocytes of the brainstem, midbrain, and hypothalamus. Serotonergic neuron 5-HT1A autoreceptors also influence the release of other monoamines, such as noradrenaline, and glucocorticoids, such as cortisol. Moreover, somatodendritic 5-HT1A autoreceptors reduce the release of 5-HT from the same neurons that express them.

5-HT1A autoreceptors are predominantly located on the soma and dendrites of neurons, whereas 5-HT1B and 5-HT2A receptors are mainly on axon terminals. Consequently, activation of these receptors fine-tunes the release of 5-HT from raphe neurons in a way that is consistent with the regulation and localization of these receptors.
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receptors

5HT1A activation in pyramidal neurons of PFC:

⇒ ↓ ERK1/2
⇒ ↓ MAP2 phosphorylation
⇒ ↓ MAP2-microtubule interaction
⇒ ↓ microtubule stability

(specifically involved with NMDA 2B subunit)

⇒ ↓ NMDAR mediated currents.

5HT2A/C counteracts these exact effects via a different pathway activating ERK1/2

5-HT projections
- Basket axon system (M fibers)
- Thin, varicose axon system (D fibers)

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Hippocampal excitatory transmission in the Cornu Ammonis based on 3 different glutamatergic pathways.

5HT fine tuning examples:
- 5HT1B at axon terminals inhibit GLU release in CA1 inhibitory interneurons:
- 5HT2/3 stimulate GABA release
- 5HT1A inhibits
Figure 3. Development and Plasticity of the Somatosensory Cortex

(A) The rodent somatosensory cortex (SSC) is characterized by one-to-one correspondence between the sensory system and its cortical projection area. Each whisker on the rodent snout is somatotopically represented in the trigeminal nucleus (termed barrelette), ventro-postero-medial thalamus (barreloid) and primary somatosensory cortex (barrel). Cortical barrels encompass a hollow center with abundant thalamocortical terminals and few granule cells in layer 4, surrounded by a ring of dense granule cells separated by septal spaces. Thalamocortical afferents (TCA) from the ventrobasal thalamic nucleus are distributed somatotopically perinatally and play an instructive role in subsequent cortical barrel field formation. Afferents-instructed barrel formation is representative of the peripheral-to-central maturation cascade, with barrelettes forming prenatally, barreloids approximately at birth and barrels around P4. Peripheral sensory input, e.g., via whisker-mediated stimuli, is critical to the organization of the barrel field during an early postnatal critical period (i.e., P0–P4).

(B) 5-HT knockout mice display a lack of characteristic barrel-like clustering of layer 4 neurons in the SSC, despite relatively preserved trigeminal and thalamic patterns. Cell bodies as well as terminals, typically more dense in barrel septa, appear homogeneously distributed in layer 4 of adult brains. Excessive concentrations of extracellular 5-HT are deleterious to SSC development suggesting that transient 5-HTT expression and its permissive action in thalamocortical neurons is required for normal barrel pattern formation in neonatal rodents, by maintaining extracellular 5-HT concentrations below a critical threshold. 5-HT1B receptors are the direct targets of excess 5-HT. While activation of 5-HT1B inhibits neurotransmitter release, specifically reducing excitatory neurotransmission in thalamocortical regions of somatosensory systems, 5-HT1B receptors act as regulators of thalamocortical development through inhibition of glutamate (GLU) release. Since normal synaptic density of 5-HT neuron terminal in SSC layer 4 of 5-HT knockout mice is maintained, it is likely that 5-HT affects SSC cytoarchitecture by promoting dendritic growth toward the barrel hollows, as well as by modulating cytokinetic movements of cortical granule cells.

(C) 5-HT also moderates activity-dependent cross-modal plasticity, a procedure of cortical restructuring to compensate for the loss of one sensory system with other intact modalities in the mature brain, specifically among the SSC and visual system. Increases in extracellular 5-HT in the rodent SSC following visual deprivation enables synaptic strengthening at layer 4 to layer 2/3 synapses in response to whisker-dependent stimulation of neural activity. The enhanced transsynaptic signaling efficiency is achieved by insertion of AMPA receptors into synapses at postsynaptic neurons through activation of the 5-HT2A/2C-dependent ERK1/2 signaling pathways and increased phosphorylation of AMPA receptor subunit GluR1, thus leading to sharpening and fine-tuning of the functional whisker-barrel map at layer 4-2/3 at an age when natural whisker experience fails to induce synaptic GluR1 delivery. LTP, long-term potentiation.
5HT and synaptic adhesion molecules (modulating synapse formation)

intracellular signaling cascades involving 5HT, GLU, neurotrophin receptors

NCAMS interact with the fibroblast growth factor receptor signaling the mTOR pathway

SHANKs connect neurotransmitter receptors, ion channels and other membrane proteins to the actin cytoskeleton

all these pathways are connected and ultimately converge on the gene transcription machinery

⇒ synthesis of structural and functional synaptic proteins
why did we look at all that?

Lont Term Facilitation in conditioned fear response and autism-linked mutation experiments

evidence supporting 5HT induced recruitment of NRXN and NLGN is implicated in long term memory formation (structural remodeling expanding synaptic connections and increasing signaling efficiency)

Choi & al. 2011
Miniaci & al. 2008
5HT modulates synaptic plasticity by influencing epigenetic modification (DNA methylation, histone mod.) through microRNA-facilitated transcriptional repression via 5HT receptor mediated activation of pathways converging on gene transcription.
take home

serotonin is implicated in all sorts of stuff, notably:
synaptic plasticity and long term potentiation

coming up

serotonin and reward (Rike)
serotonin pathology and role in punishment (Quentin)
downstream regulation of dopamine
(including serotonin glutamate interaction implicated in neurodevelopmental
disorders particularly ASD - next semester)

thanks