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Review

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A Comparison of the Subsecond Dynamics of Neurotransmission of Dopamine and Serotonin

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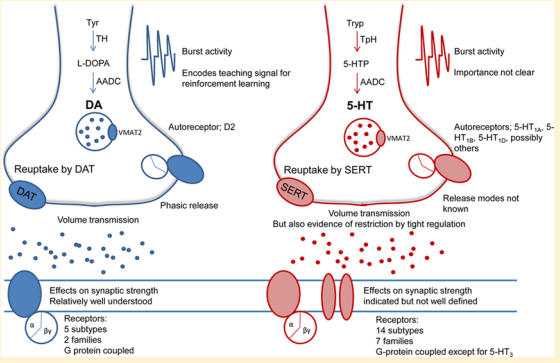
ABSTRACT: The neuromodulators dopamine (DA) and serotonin (5-hydroxytryptamine; 5-HT) are similar in a number of ways. Both monoamines can act by volume transmission at metabotropic receptors to modulate synaptic transmission in brain circuits. Presynaptic regulation of 5-HT and DA is governed by parallel processes, and behaviorally, both exert control over emotional processing. However, differences are also apparent: more than twice as many 5-HT receptor subtypes mediate postsynaptic effects than DA receptors and different presynaptic regulation is also emerging. Monoamines are amenable to real-time electrochemical detection using fast scan cyclic voltammetry (FSCV), which allows resolution of the subsecond dynamics of release and reuptake in response to a single action potential. This approach has greatly enriched understanding of DA transmission and has facilitated an integrated view of how DA mediates behavioral control. However, technical challenges are associated with FSCV measurement of 5-HT and understanding of 5-HT transmission at subsecond resolution has not advanced at the same rate. As a result, how the actions of 5-HT at the level of the synapse translate into behavior is poorly understood. Recent technical advances may aid the study of 5-HT in real-time. It is timely, therefore, to compare and contrast what is currently understood of the subsecond characteristics of transmission for DA and 5-HT. In doing so, a number of areas are highlighted as being worthy of exploration for 5-HT.



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Since the existence of serotonin (5-HT, 5-hydroxytryptamine) was confirmed in the brain 60 years ago, it has been the subject of intense study.[1] 5-HT is implicated in sensory, motor, emotional, and cognitive processing and is thought to be involved to some extent in most psychiatric disorders.[2] The most well-identified functions of 5-HT are its involvement in anxiety, depression, and impulsivity. Accordingly, a detailed knowledge of the pharmacological and cellular effects of antidepressants, anxiolytics, and other psychotropic drugs that target the 5-HT system has emerged. However, how the effects of these drugs translate into raised mood or decreased anxiety is not well understood. Furthermore, how different behavior–brain 5-HT level associations fit together remains unclear. For instance, anxiolysis on reducing brain 5-HT is well established, suggesting that 5-HT increases anxiety.[3,4] However, anxiety is often comorbid with depression which is classically associated with low 5-HT[5−7] (but see ref 8 for a thorough discussion of the conflicting findings regarding 5-HT in depression). Also, SSRIs effectively treat both disorders. Therefore, no unified relationship between 5-HT levels and behavior is yet established. Indeed, the years of research that have come before could indicate that a simple relationship does not exist. However, it is also possible that studies to date have not provided a sufficiently detailed understanding of 5-HT signaling on a time scale that is commensurate with neuronal transmission. An understanding of the detailed dynamics of 5-HT might therefore clarify how 5-HT governs behavior.

Mesostriatal dopamine (DA) transmission has been studied for a comparable length of time to 5-HT but understanding of the subsecond characteristics of DA release and reuptake, and how these dynamics shape behavior, is better defined. One reason for this is that exploration of mesostriatal DA transmission can be studied with high temporal resolution. Both 5-HT and DA are amenable to electrochemical detection using fast scan cyclic voltammetry (FSCV), which is unique in its ability to resolve release and reuptake of identified monoamines evoked by individual action potentials.[9−13] By contrast to DA, technical challenges facing the voltammetric study of 5-HT[10,14] have meant that 5-HT transmission has been traditionally studied using microdialysis, for example, refs 15 and 16. Although microdialysis studies are directly responsible for current understanding of 5-HT transmission, this technique lacks the ability to resolve individual transmission events as it samples on a time scale of many minutes. Because of this, the subsecond characteristics of 5-HT transmission are poorly understood.

Recent studies have successfully applied FSCV to the study of 5-HT in vivo. These and other technical advances (e.g.,

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optogenetics) will facilitate and renew investigation of 5-HT transmission at a subsecond resolution. Therefore, it is timely to examine where attention might be best directed. The purpose of this Review is to compare current understanding of the real-time dynamics of 5-HT and DA transmission and how such understanding has contributed to models of behavioral control. In doing so, areas worthy of exploration in the study of 5-HT transmission are highlighted. In defining the focus of the Review, it is worth noting two points. First, areas worthy of investigation are put forward only as a starting point for exploration in light of newly available techniques. The intention is not to overlook the many differences between the DA and 5-HT systems nor is it to advocate restricting the study of 5-HT within the boundaries of what is known for DA. Indeed, the fact that 5-HT is less well understood than DA could reflect physiologically relevant and fundamental differences between the two monoamine systems. Second, while current understanding of 5-HT function has been driven by its pharmacological characterization, few of these studies have focused on the subsecond dynamics of 5-HT transmission. Their discussion is therefore beyond the scope of this Review.

CHALLENGES TO EXPLORING FSCV DETECTION OF 5-HT

FSCV offers the ability to selectively identify and measure monoamine release with high temporal and spatial resolution. A voltage waveform is applied to a carbon fiber several times per second, providing a measurement of the monoamine present at the surface of the carbon fiber each time. At specific characteristic potentials in the waveform, monoamines are oxidized or reduced, producing current. The resultant voltammogram provides chemical identity as well as allowing quantification of the amount of monoamine present.[17] Measurement of 5-HT using FSCV poses a number of challenges. 5-HT adsorbs to the carbon fiber, slowing electrode response times and distorting the magnitude of measurements.[10,18] Unlike DA, 5-HT produces many oxidative side-products which also adsorb to the carbon fiber, fouling the surface and impairing 5-HT detection.[10,14] Major contributors to this fouling are ascorbic acid and 5-HIAA, the predominant metabolite of 5-HT, which is present in concentrations of up to 3 orders of magnitude higher than 5-HT in vivo.[14] Therefore, measurement of 5-HT in vivo has been technically challenging. One approach to solving this problem has been to study a model organism where fouling poses less of a problem (e.g., Drosophila[19,20]); another approach has been to modify technical parameters to optimize 5-HT detection. Modifications to the scanned waveform shape and scan rate as well as coating carbon fibers in Nafion to prevent access of side-products to the fiber have offered improvements.[10] Such modifications also selectively increase detection of 5-HT relative to 5-HIAA and DA.[14] Studies successfully applying these modifications in vivo in the substantia nigra (SNr), which receives a relatively selective 5-HT innervation, have recently been published, offering renewed promise for studying the dynamics of 5-HT transmission in the intact mammalian brain.[14,21,22] In addition to fouling problems, the pattern of brain 5-HT innervation has also contributed a challenge to in vivo FSCV measurement. While FSCV allows identification of individual monoamines, it does not allow the separate quantification of 5-HT and DA when they are simultaneously present at the electrode. Therefore, a relatively pure 5-HT or DA signal is needed for accurate measurement (see ref 23 for further discussion of the criteria for identification). 5-HT innervation is widespread throughout the brain and is often interspersed with other monoamines.[24] This means that the number of brain regions in which 5-HT can be selectively detected without contamination from other monoamines is limited. By contrast, FSCV study of mesostriatal DA has been facilitated by the fact that DA is the major monoamine detected in the striatum.

FSCV INVESTIGATION OF PRESYNAPTIC REGULATION OF DA AND 5-HT RELEASE

Influence of Neuronal Firing Patterns. DA and 5-HT neurons show different basal firing rates and regularity of firing; however, tonic and phasic firing modes have been reported in both populations. In DA neurons, tonic firing is characterized by low frequency (1−9 Hz), irregular firing[25] while phasic firing consists of high frequency bursts of 2−5 spikes. Bursts usually occur around frequencies of 20 Hz,[26,27] but frequencies above 100 Hz have been reported.[28] For 5-HT neurons, tonic firing is seen at 0.1−3 Hz, and it was classically defined as having clocklike regularity.[29,30] However, irregular and higher firing rates (up to 17 Hz) have now also been reported in subpopulations of 5-HT neurons.[31−33] 5-HT neurons also exhibit bursts of high frequency phasic activity that can be similar to those seen in DA neurons (2−4 spikes at 100 Hz or greater).[26,27,31−36] In the DA system, it is thought that bursting is as important as firing frequency for determining release and knowledge of how bursting activity changes extracellular DA ($[DA]_o$) has been essential for understanding DA function.[27,37−39] Understanding the significance of patterns of activity for 5-HT release might therefore have similar benefits for understanding 5-HT function, whether this is similar to the relationship that governs DA release or not.

Early FSCV studies exploring evoked DA in vivo demonstrated that $[DA]_o$ was related to frequency and pulse number of evoking stimulus.[39−41] A number of mechanisms ensure that bursting produces discrete, transient, and high magnitude increases in extracellular DA concentrations ($[DA]_o$), termed "phasic" release. At glutamatergic synapses, bursting causes short-term facilitation (STF) meaning release by an action potential is augmented when it closely follows another action potential; this is thought to result from summation of Ca^{2+} transients in the presynaptic terminal.[42] STF has been reported for DA release in the nucleus accumbens during burstlike stimuli and has been confirmed to be dependent on Ca^{2+} availability.[39,43] In addition to facilitating release, bursting also generates greater $[DA]_o$ through uptake dependent mechanisms. Close clustering of release events during high frequency activity reduces the time available for uptake to act on release by each pulse, thus allowing greater summation of DA released during the stimulus train.[39,44] Finally, release evoked by bursting is less likely to self-limit since the increases in $[DA]_o$ are thought to be too transient to activate autoreceptors.[45] As well as differences in the presynaptic regulation of phasic versus tonic release, the two modes are also thought to exert different postsynaptic effects, which are discussed further below.[46,47]

Given that 5-HT neurons exhibit bursts of activity, it might also be the case that discrete, phasic 5-HT release can be observed. Initial studies in vitro seemed to support this idea. FSCV measurement of 5-HT has shown that electrically evoked 5-HT does increase with frequency and pulse number in vitro.[48−52] Microdialysis measurements in vivo also show that basal 5-HT levels increase after repeated burst-like stimulation

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compared to single pulse stimulation at the same frequency.[53] However, microdialysis lacks the ability to resolve discrete phasic 5-HT release. Furthermore, one recent FSCV study has cast doubt over whether burst firing in 5-HT neurons results in phasic release as it does for DA. Modeling of electrically evoked SNr 5-HT release suggests that 5-HT released per pulse in vivo is around 50 times lower than that in vitro.[21,22,50] The authors went on to demonstrate that 5-HT release shows less fatigue during repeated stimulation and is less affected by inhibition of synthesis and packaging than DA.[21] They concluded that only a small proportion of available 5-HT is released by electrical stimulation (by comparison to DA). Collectively, these findings could suggest that 5-HT release is strictly regulated in the presence of intact circuitry, meaning that phasic 5-HT release may not result upon phasic activity. However, whether this restricted control is due to concurrent electrical activation of other circuits that inhibit 5-HT release is not yet clear. Furthermore, the SNr contains a high density of SERT protein, as well as a higher proportion of synaptic versus nonsynaptic junctional complexes compared to other regions in the brain.[54,55] Therefore, it is possible that 5-HT release in the SNr is subject to atypical regulation and differences between in vitro and in vivo measures seen in this region might not translate to others. Irrespective, the disparity between findings from slice and whole animal experiments highlights the need for further investigation of 5-HT release in vivo to identify whether discrete, burst-driven release events could be a feature of 5-HT neurotransmission.

Influence of Reuptake. The influence of both DA and 5-HT on postsynaptic receptors after release is limited by uptake from the extracellular space into the presynaptic terminal. Uptake is mediated respectively by the closely related transporters, DAT[56,57] and SERT.[58] Early in vivo FSCV studies of DA demonstrated that the influence of uptake varied depending on region and identified the striatum as an "uptake-dominated" region.[59,60] This is in contrast to areas such as the cortex and amygdala which are considered "release-dominated". A heterogeneous influence of uptake is also observed between (as well as within) the subterritories of the striatum, with uptake exerting a greater effect in the caudate putamen (CPU) than in the nucleus accumbens (NAc).[60−63]

In vivo and in vitro evidence demonstrates that DAT limits the influence of DA in a frequency-dependent way.[39,40,44,60,64−66] The short interpulse interval within bursts limits the effect of DAT-mediated uptake on release by each pulse, allowing greater summation of $[DA]_o$. By contrast during low frequency firing, uptake can more fully limit release per pulse, better preventing $[DA]_o$ summation.[65] Consistent with this role as a high frequency pass filter, DAT gene knockout abolishes frequency dependence and causes $[DA]_o$ evoked at all frequencies to be equally high; in other words, release events can summate unchecked even at low frequencies.[64]

A similar role for SERT has been reported in vitro. Under normal conditions evoked $[5\text{-HT}]_o$ shows strong frequency-dependence.[48,49,67] However, both knockout and overexpression of SERT abolish this frequency-dependence, as does SERT blockade.[49] With SERT knockout and blockade, $[5\text{-HT}]_o$ evoked by all frequencies tends toward equally high levels, while SERT overexpression constrains $[5\text{-HT}]_o$ evoked by all frequencies to equally low levels. These findings therefore mirror in vivo findings for DA and DAT, indicating that a role as a high frequency pass filter of $[5\text{-HT}]_o$ is possible for SERT. However, it is important to note that such a role for SERT has yet to be investigated in vivo. Recent studies indicating different regulation of 5-HT release between in vivo and in vitro conditions mean that the physiological relevance of this role requires direct confirmation. However, this area of exploration provides a good example of how concepts in the DA field can point to areas for investigation of the 5-HT system.

Influence of Presynaptic Receptors on Striatal DA Transmission. Two families of DA receptors have been identified: D1-like (D1Rs: encompassing D1 and D5 subtypes) and D2-like receptors (D2Rs: encompassing D2-D4 subtypes). D1Rs are positively coupled to adenylate cyclase, through G_{olf} and $G_{\alpha s}$,[68] while D2Rs negatively couple to adenylate cyclase via $G_{\alpha i}$.[69] As such, they exert opposing effects on the excitability of the cells they are expressed on (for a review of the precise coupling and effects of each receptor, see ref 69). Striatal D2Rs function as autoreceptors on DA axons and as heteroreceptors on striatal projection neurons and cholinergic interneurons (ChIs). D1Rs function as heteroreceptors on MSNs and afferent inputs into the striatum.[70,71]

FSCV and amperometry studies exploring striatal D2R autoinhibition allowed characterization of the timecourse of action on DA release.[72,73] The timecourse of activation of D2Rs reported by different studies varies from milliseconds to seconds.[45,74−79] This discrepancy might be explained by differences in preparation (in vitro versus in vivo) as well as species differences.[44] The importance of D2R control of DA release also varies according to the region of interest with more influence seen in axonal regions compared to midbrain.[75] Between midbrain regions, heterogeneity is also seen, with an autoreceptor effect observed in SNc but not in VTA.[75] Finally, variation in D2R autoinhibition is observed within regions and is hypothesized to contribute to the marked variation in release amplitude observed in the dorsal striatum.[80] Autoreceptor-induced inhibition of DA release by single pulses or very brief trains is minimal or absent, with it being most apparent during long trains of stimuli,[45,75] suggesting high enough levels of DA release and sufficient time is needed to activate autoreceptors. Effects of autoreceptor activation also appear to be most apparent at frequencies of around 20 Hz.[74,81] These observations have led to proposals that D2 autoreceptors serve two functions: First, they limit DA released by phasic activity. Second, their activation by phasic release depresses subsequent tonic release, thereby enhancing contrast between phasic and tonic release. However, this view should be contrasted with several other points. First, modeling studies suggest that occupancy of D2Rs increases little upon phasic firing (see next section).[82] Second, FSCV investigation of D2 autoinhibition has uncovered paradoxical facilitatory effects on DA release, by using repeated high frequency stimulus trains with varying interstimulus intervals.[83] The relevance of these findings for ongoing physiological patterns of activity, however, is not yet fully understood. Third, cholinergic modulation of both DA release and its short-term plasticity[84,85] is likely to be modulated by D2Rs expressed by ChIs.[70] The concerted actions of different D2R populations on DA release in vivo are therefore complex and not yet fully delineated. The mechanisms through which D2 autoreceptors limit $[DA]_o$ are also subject to ongoing investigation, although changes in release, firing and uptake are all implicated (see ref 44 for review).

Autoreceptor control of 5-HT release is of particular interest as its desensitization is thought to be important for the therapeutic effects of antidepressants.[86,87] Multiple 5-HT

autoreceptor subtypes exist. The somatodendritically localized 5-HT_{1A} subtype is the best characterized, although 5-HT_{1B}, 5-HT_{1D}, 5-HT_{1E}, and 5-HT_{1F} receptor subtypes are located on terminals and are also known to mediate autoinhibition.[88] However, delineating the individual effects of each subtype has been challenging as available ligands often bind to more than one subtype. Early FSCV studies confirmed autoinhibitory control of 5-HT release in the dorsal raphe nucleus (DRN) and suprachiasmatic nucleus (SCN), areas containing 5-HT cell bodies and axons, respectively.[24] This control, like that for DA, was only present during longer stimulations and showed frequency dependence, being most apparent at 10 and 20 Hz. By comparing different stimulus durations, the authors concluded that released 5-HT must be present for at least 400 ms to activate autoreceptors.[52] Further FSCV characterization of these effects has shown that ligands at 5-HT_{1A} receptors best affect 5-HT release in the DRN, although a lesser control by 5-HT_{1B} and 5-HT_{1D} receptors is also present. By contrast, control in SCN appears to be mediated by 5-HT_{1B} and 5-HT_{1D} receptors as ligands at these receptors best affected 5-HT release in this region.[89−92] In the SNr, a modest control by 5-HT_{1B} receptors has been reported, although this is only seen during specific time windows.[93,94] Thus, Threlfell et al. demonstrated that 5-HT_{1B} receptor-mediated short-term depression of 5-HT release could be observed when stimulus trains were paired 2 s apart.[94]

FSCV investigation of 5-HT autoinhibition is challenging in vivo because the effects of multiple autoreceptor subtypes at different locations may interact. However, this will be an important part of understanding how 5-HT transmission is controlled, since activation of autoreceptors will likely vary between in vivo and in vitro conditions, due to differences in 5-HT tone. Indeed, the study of DA autoreceptor function implies different findings may be seen between in vivo and in vitro conditions.[44] FSCV used in conjunction with selective optogenetic stimulation strategies may aid in overcoming the challenges presented by studying autoinhibitory control of 5-HT in intact circuitry.

DIFFERENT MODES OF RELEASE MAY CAUSE DISTINCT POSTSYNAPTIC EFFECTS

Understanding gained from FSCV study of DA has directly contributed to an important concept in the field of striatal DA function, namely, that different modes of DA release cause distinct postsynaptic effects. This realization allowed understanding of how a broadcast DA signal that was not restricted by the conventions of synaptic transmission could still convey highly specific information. DA exerts effects on two major populations of striatal projection neurons (medium spiny neurons; MSNs), each one preferentially expressing one subtype of DA receptor. Direct pathway MSNs express D1Rs and project to the substantia nigra where they promote movement by disinhibiting the thalamus. Conversely, indirect pathway MSNs express D2Rs and inhibit movement.[95−98] Together, these observations support the classical model of dopamine function whereby DA promotes movement through a D1R-dependent increase in direct pathway excitability and a D2R-dependent reduction of indirect pathway excitability.[69,99,100] It is worth noting that a recent study demonstrated concurrent activation of direct and indirect MSNs upon movement initiation.[101] This finding is not necessarily at odds with the idea that the indirect pathway suppresses movement; however, how it fits with what is understood of how DA affects these pathways, discussed below, remains to be seen.

D1Rs exhibit low affinity for DA, while D2Rs are largely found in a high affinity state (EC_{50} ∼ 1 μM and ∼10 nM, respectively).[102] Estimates of affinity constants and understanding of diffusion and uptake characteristics of DA release from FSCV[40,41,103−105] have supported the idea that the different receptors might be preferentially activated by distinct modes of DA release.[106] Dreyer et al. formalized this model by simulating DA receptor occupancy during tonic and phasic firing. They found that D2R occupancy was steady during tonic firing but reduced during phasic firing and pausing. Conversely, D1Rs were unoccupied during tonic firing but occupancy increased on phasic firing.[82] Supporting the idea that distinct modes of firing have distinct postsynaptic consequences, increasing phasic firing in DA neurons in vivo causes D1R-dependent facilitation of evoked neural responses in ventral striatum, while increasing tonic firing does not. Furthermore, blocking D1Rs without increasing phasic DA activity has no effect, suggesting that the receptors are not tonically active.[107,108] Given that direct MSNs selectively express D1Rs, it is possible that phasic DA release may serve to activate this pathway selectively and promote movement. The importance of phasic DA release for reinforcement learning is well established, but a role in movement initiation is only beginning to emerge.[109,110] Therefore, understanding of the dynamics of DA transmission gained through FSCV continues to add to theories of motor control.

In addition to the activation of functionally distinct neuronal populations, models of DA volume transmission derived from FSCV data also predict distinct spatial patterns of influence by different modes of DA release. Because DA diffuses extrasynaptically,[40,104] a concentration gradient is established on release that declines with distance from the release site and time from the release event.[46,47,111] Activation of receptors by released DA will be determined by $[DA]_o$ and receptor affinity. Assuming that $[DA]_o$ must equal or exceed the receptor EC_{50}, Cragg and Rice defined the respective maximum spheres of influence of DA at high (D2Rs) and low (D1Rs and some D2Rs) affinity receptors as 7 and <2 μm.[46,47] Taken together, the above studies have allowed understanding of how DA signals that are seemingly globally broadcast via volume transmission can produce a surprisingly degree of spatial and functional target specificity.

In excess of 14 5-HT receptors have been identified to date, which are grouped into 7 families (5-HT_1−5-HT_7).[8,88] Because of this pharmacological complexity, receptor affinities are often characterized in terms of specific ligands, rather than for 5-HT itself. However, a small number of early studies show that 5-HT_2 receptors have a lower affinity for 5-HT than 5-HT_1 receptors, giving a K_i in the micromolar range.[112,113] Furthermore, 5-HT_6 and 5-HT_7 receptors have extremely high affinity for 5-HT (K_i ∼ 5 nM[114]), which exceeds that of 5-HT_1 receptors by an order of magnitude.[114,115] Therefore, evidence suggests that the affinity of different 5-HT receptors for 5-HT spans at least 2−3 orders of magnitude.

Zero net flux microdialysis studies estimate basal 5-HT levels to be between 0.5 and 7 nM, depending on the species and brain region.[116−121] Therefore, it is possible that ambient $[5\text{-}HT]_o$ may be low enough to leave unoccupied all but the highest affinity receptors during tonic firing (but see caveat below). This means that increases in 5-HT levels, whether they result from bursting or sustained increases in firing, might

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target different populations of receptors and/or neurons. In addition, 5-HT_{2A} and 5-HT_{1A} receptors, which are coupled to different signaling cascades and have different affinities for 5-HT, have been colocalized to the same forebrain pyramidal cells.[122] This raises the interesting possibility that 5-HT might produce different effects on the same cell according to the magnitude of release. In this example, moderate increases in 5-HT could modulate pyramidal cell activity via 5-HT_{1A} cells, while larger increases in 5-HT might also cause 5-HT_{2A} receptor-mediated changes in excitability. Therefore, fundamental features exist within the 5-HT system that could allow different levels of 5-HT to target distinct pathways selectively or to affect the same neuron differently. Note though that additional factors will influence whether receptors are activated (e.g., proximity to release sites), and therefore, modeling studies will be needed to explore this further. However, if it holds, such a possibility could in part explain the diversity of behaviors influenced by 5-HT.[123] As a caveat to this argument, it is noteworthy that no-net-flux estimates of $[DA]_o$ have been shown to underestimate DA levels due to tissue damage caused by the large probe size.[124,125] This raises the possibility that current estimates of $[5\text{-HT}]_o$ are inaccurate. Therefore, FSCV studies establishing basal and evoked $[5\text{-HT}]_o$ will be important in determining whether differential activation of 5-HT receptors by different levels of $[5\text{-HT}]_o$ is plausible. Investigation of the postsynaptic effects of specific 5-HT receptor subtypes should also be aided by improved design of specific ligands resulting from recent studies.[126]

FSCV study of 5-HT transmission will allow understanding of the distinct dynamics governing 5-HT transmission and allow a more dynamic picture of 5-HT transmission to emerge. In turn, this should allow a better framework for understanding how 5-HT governs brain function and behavior.

Modulation of Activity-Dependent Plasticity: Distinct Roles of Different Receptors. The above section discussed the ways that exploration of the subsecond dynamics of DA transmission has facilitated modeling of how DA activates postsynaptic neurons to mediate movement. In addition, these concepts have combined with data from electrophysiology studies of synaptic plasticity to inform ideas on how DA mediates learning. 5-HT also exerts control over activity dependent changes in synaptic strength, although these effects appear to be conflicting and complicated. Better understanding of the action of 5-HT on synaptic strength may contribute to understanding how it mediates control of behavior at a synaptic level.

In the striatum, DA controls plasticity at synapses between excitatory cortical inputs and MSNs by determining whether a synapse will show potentiation or depression.[127] Early studies suggested that, in contrast to other regions, plasticity in the striatum required DA.[128,129] Furthermore, evidence suggested that D1Rs were necessary for long-term potentiation (LTP[130−132]), while D2Rs were necessary for long-term depression (LTD)[128,133,134] (although see refs 135 and 136 for full reviews of the topic). Given that direct MSNs preferentially express D1Rs and indirect MSNs preferentially express D2Rs, these findings seemed to suggest that only one direction of plasticity would be seen in each population of MSNs. Studies have since demonstrated the existence of bidirectional plasticity in both direct and indirect MSNs.[127,135,137,138] In a seminal study, Shen et al. demonstrated that D1Rs were indeed important for LTP in direct MSNs but that LTP in indirect MSNs was mediated by adenosine 2a receptors.[127] This group also showed that D2Rs mediated LTD, but that the D2Rs responsible are most likely located on cholinergic interneurons and thus the requirement of D2R activation for LTD does not preclude its expression in both MSN populations.[127,139] Therefore, DA is not required for plasticity to occur but rather, the balance of D1R/A2a and D2R activation determines whether it is LTP or LTD that is expressed. Understanding of DA-modulated plasticity has had important consequences for understanding how DA release modes govern learning at the synaptic level.

Given that D1Rs may be preferentially activated by phasic DA release, it might be predicted that phasic DA release would promote LTP. This is supported to some extent by the fact that transient, pulsatile DA application (which more closely mimics phasic DA release than bath application)[140] and phasic stimulation of DA neurons[130] lead to LTP, rather than LTD.[141] Findings overall support an important role for DA in modulating synaptic plasticity. Additionally, the DA receptors involved and the prevailing mode of DA release may dictate whether synaptic strength is depressed or potentiated. These concepts have fostered the current view of reward learning and action selection: phasic DA release elicited by reward acts upon active synapses that are mediating movement to promote LTP and learning of the movement. By contrast, synapses mediating unsuccessful actions undergo LTD.[135,142] Although this view is likely still oversimplified, it illustrates how knowledge of DAergic control of synaptic plasticity has informed understanding of behavioral control.

A reasonable body of evidence implicates 5-HT in modulating activity-dependent changes in the strength of mammalian central synapses (see below). Furthermore, molecular machinery by which 5-HT could influence LTP is now identified.[143] However at present, existing studies are too few to provide a clear picture of how 5-HT controls activity-dependent plasticity.

Early studies in cat visual cortex implicated 5-HT_{2C} receptors in the facilitation of activity-dependent plasticity. At first however, their precise involvement was unclear: in around half of cases, 5-HT receptor activation during induction would result in LTP, while in the other half LTD was seen. It was subsequently shown that the direction of plasticity depended on whether there was a high density of 5-HT_{2C} receptors present (LTP) or a low density (LTD).[144−147] Plasticity has also been investigated in rat visual cortex, and hippocampus. Overall, studies show that 5-HT_{1A}, 5-HT_{2A}, and 5-HT_4 receptors are important but can either inhibit[148−155] or facilitate plasticity.[145,148,156,157] Interestingly, such findings are reminiscent of the apparent conflict in early findings of D1- and D2-dependence of LTP and LTD, as well as of the literature concerning 5-HT_{2C} modulation of plasticity discussed above. Therefore, it is possible that variable receptor density or involvement of distinct receptors under different experimental conditions may explain the variability in findings. Improved understanding of how 5-HT modulates synaptic plasticity would be of great use in modeling its role in emotional learning.

MEASUREMENT OF TRANSMISSION IN REAL-TIME DURING BEHAVIOR: INSIGHTS INTO BEHAVIORAL CONTROL

A large body of work has detailed the effects of 5-HT manipulations on behavior. However, assigning a specific role for 5-HT in behavioral control has been problematic. 5-HT is implicated in many behaviors, with the most notable being

behavioral inhibition, anxiety, and depression. Although relationships exist describing how 5-HT levels relate to each of these behaviors, no clear unified theory has emerged that easily incorporates all of these relationships. The animal literature strongly suggests that 5-HT is anxiogenic, while lowering 5-HT precipitates depression in vulnerable individuals. And yet anxiety and depression are often comorbid and chronic inhibition of 5-HT uptake effectively treats both anxiety and depression.[3,4,158−160] Furthermore, simple decreases in 5-HT levels do not induce depression in healthy individuals, nor does elevating 5-HT immediately alleviate depression in patients.[5,86] In the case of impulsivity, different 5-HT receptor subtypes appear to have opposing effects on the same impulsivity measures.[161] Direct correlation of online, real-time 5-HT release would greatly aid understanding of how 5-HT controls behavior. Unfortunately, to date, technical challenges have precluded such studies. Instead, electrophysiology has been employed to correlate 5-HT firing patterns with behavior, although these studies are not without their challenges. This section will discuss these challenges further after summarizing current understanding of how firing patterns correlate with behavior.

Early electrophysiology studies correlating DA neuron activity with behavioral events showed that phasic DA activity behaved as a reward prediction error used by reinforcement learning algorithms. Thus, DA neurons show phasic firing in response to better-than-expected outcomes and pause in response to worse-than-expected outcomes.[37,162−164] Combined with knowledge of how firing translates into DA release and DA-mediated control of synaptic plasticity, this finding greatly aided understanding of how the actions of DA at a synaptic level might govern reward-related and motor learning to modulate behavior. Subsequent in vivo FSCV studies confirmed that phasic DA release is elicited under similar circumstances to phasic firing and is both necessary and sufficient for reward seeking behavior.[110,165−167] Additional information carried in DA signals, such as reward value and risk, has also been reported.[168−170] In addition to a well-established role in reward, a minority of DA neurons show phasic activation to aversive events.[171−174] These neurons are distinct from reward-activated DA neurons and are found in different anatomical locations.[171−173] The characteristics of these subpopulations and their precise anatomical targets are yet to be fully explored. However, it seems possible that these DA neurons mediate aversion learning in distinct brain regions to reward learning but through similar effects on synaptic plasticity.

Many studies have correlated 5-HT neuron activity with behavioral events. Early studies examined spontaneous behavior and ascribed a role for 5-HT neuron activity in attention. Putative 5-HT neurons showed phasic increases in activity in response to short, unexpected visual and auditory stimuli.[175,176] However, other studies reported that such cells were unresponsive to stimuli that would be expected to attract attention such as loud noises, predator exposure and restraint.[177] A sensorimotor role for ascending 5-HT neurons has also been hypothesized as cells show increased firing to sensorimotor parameters during operant responding (e.g., direction of response[178]) as well as during putative central pattern generator-mediated movements, e.g. chewing, licking, biting and grooming.[179] More recently, a correlation of neural activity with reward and/or aversion has been reported that is predicted by a large literature detailing anxiety and aversion in response to pharmacological manipulations of 5-HT.[158,180] In anesthetized rats, phasic activation in response to an "aversive" toe-pinch has been reported,[35] while during behavior studies have found that firing tracks progress to future reward[181] and received reward value.[178,182] These results have led to theories that 5-HT serves as a companion or opponent to DA in reward processing.[158,159] However, other studies have reported no response to reward, reward omission, or aversive events.[178,183,184] A slightly different take on 5-HT in reward processing is that 5-HT transmission is necessary for waiting, either to gain reward or to avoid punishment. During delayed reward delivery, tonic firing of 5-HT neurons increases during the waiting period and ceases immediately preceding an animal leaving the reward port.[183] Treatment with a drug that dampens 5-HT neuron firing decreased waiting for reward in this task.[185] This group advanced the idea that 5-HT serves in reinforcement learning to discount future rewards and punishments, representing the discount factor in the same reinforcement learning algorithm that incorporates the reward prediction error that DA encodes.[186,187]

A key difficulty for identifying physiologically relevant responses in 5-HT neurons is understanding which neuronal responses are meaningful for transmission. Recent FSCV studies suggest that 5-HT release is under very strict regulation in vivo.[21] Therefore, it is possible that brief and/or modest changes in firing frequency may have little or no influence on 5-HT release. FSCV determination of the possible modes of 5-HT release in vivo will therefore be beneficial for interpreting findings of electrophysiological studies of 5-HT neurons during behavior.

An additional challenge for correlating neural activity with behavior is correct identification of 5-HT neurons. Increasing evidence suggests that the population of DRN 5-HT neurons is highly heterogeneous and exhibits no single "signature" of electrophysiological characteristics.[188] Recent studies have shown that non-5-HT cells can exhibit similar characteristics to those classically used to identify 5-HT cells (slow spiking, broad action potential, clocklike firing[30]) and vice versa.[33,36,189] Although juxtacellular labeling has been incredibly informative for identifying such heterogeneity, applying this technique after behavioral studies to identify recorded cells is difficult. Recently, optogenetics has been applied to identify subtypes of electrophysiologically identical cells in vivo.[190] Therefore, this approach may prove fruitful in studying 5-HT.

■ CONCLUSIONS AND FUTURE DIRECTIONS

Understanding DA transmission on a time scale commensurate with neuronal signaling events has facilitated progress toward an integrated model of how DA governs behavior. Similar understanding of subsecond 5-HT signaling has been hampered by technical challenges but is now beginning to emerge. This Review has compared what is known of the subsecond dynamics of DA and 5-HT transmission and how these are thought to relate to behavioral control in the case of DA.

FSCV characterization of the dynamics and regulation of 5-HT release in vivo will be important for establishing whether distinct modes of 5-HT release occur, as well as for providing estimates of basal 5-HT levels in the absence of potentially confounding tissue damage. In turn, this information will inform on whether different modes of 5-HT release might mediate distinct postsynaptic effects, as is likely for DA. Furthermore, FSCV data will serve as an important companion to electrophysiology studies correlating activity with behavior,

by informing on physiologically meaningful changes in 5-HT activity. Understanding whether and how 5-HT controls activity-dependent plasticity may also aid in understanding how it governs behavior. In addition, application of newly developed optogenetic technology will greatly aid the study of the 5-HT system. First, it will facilitate FSCV investigation of 5-HT by allowing selective stimulation of 5-HT release in brain regions receiving input from multiple monoamines. Second, it will allow accurate identification of 5-HT cells in electrophysiological experiments correlating activity with behavior. Establishment of fundamental aspects of 5-HT release and how these relate to firing patterns at high temporal resolution should ultimately advance understanding of 5-HT function in health and disease and enable improved treatment of serotonin-related disorders, such as depression and anxiety.

AUTHOR INFORMATION

Notes

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