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Perspective

Abnormal Neurotransmitter Release Underlying Behavioral and Cognitive Disorders: Toward Concepts of Dynamic and Function-Specific Dysregulation

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Abnormalities in the regulation of neurotransmitter release and/or abnormal levels of extracellular neurotransmitter concentrations have remained core components of hypotheses on the neuronal foundations of behavioral and cognitive disorders and the symptoms of neuropsychiatric and neurodegenerative disorders. Furthermore, therapeutic drugs for the treatment of these disorders have been developed and categorized largely on the basis of their effects on neurotransmitter release and resulting receptor stimulation. This perspective stresses the theoretical and practical implications of hypotheses that address the dynamic nature of neurotransmitter dysregulation, including the multiple feedback mechanisms regulating synaptic processes, phasic and tonic components of neurotransmission, compartmentalized release, differentiation between dysregulation of basal *vs* activated release, and abnormal release from neuronal systems recruited by behavioral and cognitive activity. Several examples illustrate that the nature of the neurotransmitter dysregulation in animal models, including the direction of drug effects on neurotransmitter release, depends fundamentally on the state of activity of the neurotransmitter system of interest and on the behavioral and cognitive functions recruiting these systems. Evidence from evolving techniques for the measurement of neurotransmitter release at high spatial and temporal resolution is likely to advance hypotheses describing the pivotal role of neurotransmitter dysfunction in the development of essential symptoms of major neuropsychiatric disorders, and also to refine neuropharmacological mechanisms to serve as targets for new treatment approaches. The significance and usefulness of hypotheses concerning the abnormal regulation of the release of extracellular concentrations of primary messengers depend on the effective integration of emerging concepts describing the dynamic, compartmentalized, and activity-dependent characteristics of dysregulated neurotransmitter systems.
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INTRODUCTION

Over 50 years ago, Woolley and Shaw (1954) noticed the structural similarities between ergot alkaloids and serotonin ('the latest hormone-like substance to be discovered'; p. 228), and suggested that because of the 'mental disturbances' produced by some alkaloids, 'deficiency of serotonin may contribute to the production of some mental disorders' (p. 230). Contemporary hypothesis describing neurotransmitter abnormalities underlying neuropsychiatric disorders have continued to characterize these abnormalities in terms of steady-state deviations from normal levels of neurotransmitter release or extracellular concentrations of neurotransmitters. For example, '…too much dopamine in critical regions in the brain, or too little glutamate…' (Fischbach, 2006; p. 734) has been widely hypothesized to contribute to the manifestation of the psychotic and cognitive symptoms of schizophrenia (see also Laruelle *et al*, 2003). Likewise, increased or sensitized release of dopamine in striatal regions has been closely linked with compulsive drug seeking behavior (eg, Everitt and Robbins, 2005; Robinson and Berridge, 2003). Other examples include the abnormally low levels of cholinergic neurotransmission, considered to represent an essential variable in the manifestation of dementia (Mesulam, 2004), or abnormally high levels of cholinergic transmission, reflecting a disinhibited cortical cholinergic input system, which has been hypothesized to contribute to the impairments in the filtering of irrelevant stimuli in schizophrenia (Sarter, 1994; Sarter *et al*, 2005).

Based largely on the main pharmacological properties of serotonin and noradrenaline uptake inhibitors used for the treatment of depression, deficient extracellular levels of these monoamines have long been hypothesized to play a key role in the development of the core symptoms of this disorder (Berton and Nestler, 2006; Mongeau *et al*, 1997; Schildkraut, 1965). Furthermore, the antidepressant actions of a wide range of compounds acting on opioid, galanin, or

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cannabinoid receptors have formed the basis for suggestions that abnormal levels of these neurotransmitters/neuromodulators contribute to the symptoms of depression. In addition, the demonstration of the behavioral and cognitive symptoms, as a result of the administration of drugs that attenuate increases in neurotransmitter release or their postsynaptic effects, such as the detrimental cognitive effects of nicotinic and muscarinic receptor antagonists, or the depression-like symptoms resulting from acute tryptophan depletion (eg, Booij *et al*, 2005; Ellis *et al*, 2006), have been interpreted as supporting the hypothesis that abnormal levels of neurotransmitter release play a major role in the development of the cognitive, behavioral, and affective symptoms of major disorders.

As will be pointed out below, these hypotheses rarely capture the dynamic neurochemical characteristics and long-term consequences of abnormalities in the regulation of synaptic neurotransmitter release. Furthermore, the nature of the dysregulation of the release of a neurotransmitter may substantially differ, depending on whether basal or activated levels of neurotransmission are studied, and on whether the neuronal system of interest is recruited by ongoing behavioral/cognitive activity. Following a brief and general description of the dynamic consequences of alterations in the regulation of neurotransmitter release, we will discuss the methodological and experimental variables which *a priori* have favored hypotheses describing abnormal neurotransmission in terms of aberrant, steady-state increases or decreases in neurotransmitter release and/or extracellular levels. Furthermore, we will suggest that the overwhelming focus on measures of basal neurotransmitter release, as opposed to determining the nature of dysregulated release in activated neuronal systems, has favored such hypotheses. Finally, several examples will illustrate the significance of recruiting neuronal systems by relevant behavioral and cognitive activities to reveal neurotransmitter dysfunctions. A better understanding of the degree, nature, and significance of neurotransmitter dysfunctions, and of the therapeutic efficacy of drugs aimed at normalizing neurotransmitter release and levels, requires the combination of new techniques for the sub-second, spatially-restricted measurement of neurotransmitter release and psychobiological research approaches that focus on the characterization of dysregulated target systems and associated neuronal circuits in interaction with behavioral performance mediated via these systems and circuits.

ASPECTS OF DYNAMIC DYSREGULATION: FEEDBACK MECHANISMS, VOLUME AND WIRED NEUROTRANSMISSION, PHASIC AND TONIC COMPONENTS OF NEUROTRANSMISSION

The basic steps regulating synaptic neurotransmission, including the presynaptic neurophysiological and intracellular signaling mechanisms that control the neurotransmitter synthesis, storage, and release, the regulation of relevant transporters, and presynaptic and postsynaptic signaling pathways are described elsewhere (eg, Cooper *et al*, 2003). Abnormal release at a given synapse may result from a myriad of dysregulatory or structural events, organizational aberrations and persistently abnormal afferent activity. The long-term consequences of abnormal release levels are necessarily dynamic and dependent on the state of the neuronal circuit.

A brief example serves to illustrate this point. Extensive evidence has indicated an abnormal regulation of the cortical cholinergic input system before the onset of Alzheimer's disease (Dubelaar *et al*, 2006; Mufson *et al*, 2000, 2002) and, therefore, supported the hypothesis that the onset and rapid decline of elementary cognitive abilities is due in part to the decline in cholinergic neurotransmission (Mesulam, 2004; Sarter and Bruno, 2004). Although information concerning the status of cholinergic neurotransmission, including the capacity of the crucial choline transporter in this early stage of dementia, has remained scarce, let us assume that depolarization-induced acetylcholine (ACh) release is decreased. Certainly, contemporary efforts to halt cognitive decline by administering acetylcholinesterase inhibitors (Koontz and Baskys, 2005) correspond with this scenario. However, an enormous number of neuropharmacological and cellular consequences would be expected to interact with decreases in ACh release levels and yield complex consequences not in line with straightforward suggestions about disease-related changes in neurotransmitter levels. These consequences include: (a) altered regulation of different ACh storage pools; (b) altered negative feedback via presynaptic muscarinic receptors; (c) altered cholinergic stimulation of nicotinic acetylcholine receptors (nAChRs), the majority of which are heteroreceptors and influence the release of other neurotransmitters, many of which in turn modulate ACh release through local circuits and synaptic mechanisms; (d) altered stimulation of postsynaptic nAChRs and muscarinic receptors which, via long-loop mechanisms, can influence the excitability of cholinergic neurons and the synaptic regulation of ACh release. Importantly, the nature of these consequences may depend fundamentally on the level of recruitment of the cholinergic system and its main afferent circuits (see further below for examples and discussion of this issue). Clearly, the mere listing of the putative dynamic consequences of alterations in release levels suggests that descriptions in terms of one-dimensional decreases or increases in singular transmitter release or extracellular transmitter levels do not capture the true nature of neurotransmitter abnormalities and related synaptic dysregulation.

The evolving recognition that several neurotransmitter systems, under certain conditions, exhibit the capacity to act in part outside the boundaries of synapses ('volume-transmission'; Agnati *et al*, 2006; Bunin and Wightman, 1998, 1999; Callado and Stamford, 2000; Chazal and Ralston, 1987; Descarries and Mechawar, 2000; Fuxe and Agnati, 1991; Fuxe *et al*, 2005), presents an even wider range of potential feedback mechanisms involving, for example, somatodendritic autoreceptors (Cragg and Greenfield, 1997) or extra-synaptic postsynaptic receptors. Thus, abnormal regulation of neurotransmitter release likely entails differential consequences on extrasynaptic (volume) *vs* synaptic (wired) neurotransmission. These issues have been studied particularly extensively with respect to the dopaminergic system. Extrasynaptic actions of dopamine (Fuxe and Agnati, 1991) are prominent in brain regions such as prefrontal cortex of rats, which feature an overall low number of dopamine transporters and a high

proportion of transporters situated outside synapses (Sesack *et al*, 1998). Furthermore, different dopamine receptors appear to be postsynaptic to dopaminergic *vs* non-dopaminergic terminals (Smiley *et al*, 1994). These findings suggest that abnormalities in neurotransmitter release involve different extracellular concentrations in different neuronal compartments and therefore different post-synaptic signaling patterns via different dopamine receptors (see also Sesack *et al*, 2003; Trantham-Davidson *et al*, 2004).

The tonic/phasic model of dopamine release (Grace, 1991; Floresco *et al*, 2003; Thompson *et al*, 2004) describes how diverse innervation patterns give rise to different modes of neurotransmission. Phasic dopamine release is considered to reflect mainly impulse flow and result from burst firing, and it represents largely a synaptic event. The consequent high levels of extracellular dopamine are then able to activate receptor subtypes populations (ie D1-like receptors) with lower affinities for dopamine. On the other hand, tonic levels of dopamine release have been thought to result from local depolarization by non-dopaminergic afferents and to act mainly extra-synaptically. The resultant increases in extracellular dopamine primarily interact with higher affinity D2-like receptor subtypes. Although the two components interact functionally, recent evidence has shown that the tonic and phasic components of dopamine release in mesolimbic regions are controlled by separate afferent systems (Goto and Grace, 2005a, b; Lodge and Grace, 2006). As abnormal dopamine release in disorders such as schizophrenia has been hypothesized to be 'imported' as a result of abnormally constructed, telencephalic circuitries, it is likely that the two components of dopaminergic neurotransmission are differently affected, thereby yielding hypotheses suggesting dynamic aberrations of the normal interplay between tonic and phasic dopamine release.

TRADITIONAL MEASURES OF NEUROTRANSMITTER RELEASE/LEVELS FAVOR CONCLUSIONS IN TERMS OF STEADY-STATE ABNORMALITIES IN NEUROTRANSMISSION

The discussion above illustrates that hypotheses describing steady-state increases or decreases in neurotransmitter release or extracellular neurotransmitter levels are of limited heuristic significance. However, such hypotheses have remained persistent and popular, particularly in psychopharmacological research (eg, Pliszka, 2005). As will be pointed out later, the traditional methods used to generate neurochemical markers of the state of synaptic activity in patients or animal models of neuropsychiatric or neurodegenerative disorders favor such conclusions in terms of steady-state changes in neurotransmission, particularly if employed in combination with neuropharmacological tools such as transporter reversers, re-uptake blockers, metabolic enzyme inhibitors, and receptor agonist or antagonists.

Evidence concerning abnormal levels of neurotransmission in patients and animal models has mainly been generated by using the following methods: (a) Historically and presently, abnormal levels of neurotransmitters or neurotransmitter metabolites in the cerebrospinal fluid (CSF) or plasma of patients have been interpreted as indicating abnormal brain levels. Recent examples include the demonstration of abnormally high levels of the endocannabinoid anadamide (Giuffrida *et al*, 2004) and the endogenous NMDA receptor antagonist kynurenate (Erhardt *et al*, 2003) in the CSF of first episode paranoid schizophrenics, or high plasma serotonin levels as markers for psychopathology and suicidality (Tyano *et al*, 2006). Although changes in peripheral markers of brain neurotransmitter concentrations may result from increased burst firing of neurons, these measures *per se* are not capable of indicating the contribution of phasically active neurons, and thus favor conclusions in terms of steady-state changes in neurotransmitter synthesis and/or extracellular concentrations.

(b) Measurements of evoked neurotransmitter release from slices or synaptosomal preparations obtained from human or animal tissue. These methods typically include radio-labeled (usually tritium) precursor loading and electrical or neurochemical depolarization and the subsequent measurement of tritium overflow. For example, electrically-evoked ACh release from human neocortical slices was demonstrated to decrease with age (Feuerstein and Seeger, 1997). Although the nature of the stimuli used in these studies potentially allow the dissociation of effects of different modes of neuronal activity, the available evidence indicates that overflow data obtained from brain tissues from patients, animals modeling disorders and/or treated with drugs, typically have been interpreted as indicating aberrant tonic levels of neurotransmission (eg, Engler *et al*, 2006; Roberts *et al*, 2005).

(c) *In vivo* microdialysis. The microdialysis method has remained a highly popular method for the measurement of extracellular neurotransmitter concentrations in animal models and, in recent years, also in patients (eg, Hutchinson, 2005). Hypotheses concerning altered neurotransmitter levels in neuropsychiatric disorders have gained extensive support from evidence generated by microdialysis experiments in animal models (eg, Dazzi *et al*, 2001; Di Chiara *et al*, 1999; Evans *et al*, 2006; Laplante *et al*, 2004; Nelson *et al*, 2000; Rada *et al*, 2006; Segal and Kuczenski, 1997). Although evolving analytical techniques have shortened the length of dialysate collection intervals required for obtaining detectable analyte levels (eg, Sandlin *et al*, 2005), several minutes of collection are needed in most cases. During this time, brain molecules diffuse into the perfusate and, therefore, individual data points represent a proportion of the total amount of neurotransmitter released and accumulated over the collection interval. Although the interpretation of data generated by microdialysis, in terms of neurotransmitter release, can be confounded by nonlinear relationships between levels of neurotransmitter release and the rate of diffusion into the perfusate and, depending on the neurotransmitter system, dynamically regulated neurotransmitter clearance mechanisms (eg, Melendez *et al*, 2005; Smith and Justice, 1994; Vinson and Justice, 1997), evidence from microdialysis studies has been consistently interpreted in terms of steady-state alterations in neurotransmitter release.

More insight into the exact nature of the release monitored by microdialysis was gained by our recent effort to reconstruct microdialysis data (on the release of cortical ACh in task-performing rats), based on second-to-second amperometric recordings of cholinergic activity, using

enzyme-selective microelectrodes in rats performing the same task (this method and related experiments are described in more detail below in the section on 'Impact on the development of pharmacotherapeutics' below; Parikh *et al*, 2006). These analyses support the conclusion that the release measured by microdialysis reflects primarily the slow changes in neurotransmitter release that begin with task onset and last throughout the behavioral test session. In contrast to stimulus-evoked phasic increases in cholinergic activity (see below), such slow or tonic changes in neurotransmitter release were observed in multiple cortical regions, and may indicate changes in general arousal or cortical readiness for input processing (eg, Pribram and McGuinness, 1975). It is important to note that presently there is no evidence that would allow the conclusion that these slow changes in neurotransmission, which are measured by microdialysis, are of lesser functional significance than stimulus-evoked, phasic, or transient changes in neurotransmission. However, these data specify the nature of behavior-associated changes in neurotransmitter release as measured by microdialysis.

Furthermore, it is important to note that such slow or tonic changes in neurotransmitter release are highly sensitive to regulatory mechanisms, and can thus provide important insights in the dynamic regulation of neurotransmitter release in pathological states or following drug treatment. In this context, the demonstration of dissociations between neurotransmitter release observed at baseline ('basal release') *vs* release observed during activation of the neuronal system of interest ('activated release') are of particular significance and will therefore be addressed separately further below.

(d) Single photon emission computed tomography (SPECT), positron emission tomography (PET), and other non-invasive imaging methods. The demonstration that administration of amphetamine in schizophrenic patients resulted in a greater displacement of the binding of a dopamine D2 radiotracer, by SPECT or PET, provided strong support for the hypothesis that a 'hyperdopaminergic state' contributes to the symptoms during onset and subsequent periods of illness exacerbation (Abi-Dargham *et al*, 1998; Breier *et al*, 1997; Laruelle, 2000; Laruelle *et al*, 1996, 1999). However, given that these studies require a pharmacological or behavioral challenge to demonstrate differences in radioligand displacement between groups of subjects, this evidence also indicates that the neurotransmitter dysfunction is revealed by activating the system of interest (below). Radioligands for the non-invasive measurement of the release of other neurotransmitters in humans are presently being developed (eg, Ding *et al*, 2006; Roger *et al*, 2006).

These methods will continue to generate crucial information about the state of neurotransmission in disorders ranging from schizophrenia to depression and to neurodegenerative diseases. However, the structure of the evidence generated by these methods unavoidably contributes to hypotheses describing, in rather static terms, abnormal levels of neurotransmitter release, and supporting the focus of pharmacological treatment approaches on attenuation of such steady-state aberrations in neurotransmitter levels. Such hypotheses and treatment strategies do not sufficiently capture the dynamic, compartmentalized, and diverse mechanisms that control release and extracellular neurotransmitter levels, which are differentially influenced by pathological events or drug treatments. As will be discussed later, the state of the neurotransmitter system of interest, and therefore the subjects' behavioral and cognitive activity, represents a primary variable in research designed to reveal the normal and abnormal dynamics of neurotransmitter release.

BASAL *VS* ACTIVATED NEUROTRANSMITTER RELEASE

The effects of therapeutically efficacious compounds on neurotransmitter release and/or extracellular neurotransmitter levels have contributed substantially to the development of hypotheses describing abnormal levels of neurotransmitter release as a major mechanism underlying the manifestation of behavioral and cognitive impairments. The monoamine hypothesis for depression represents the main example as it has been deduced largely on the effects of monoamine uptake inhibitors on extracellular neurotransmitter levels.

An overwhelming number of studies designed to measure neurotransmitter release following the administration of therapeutic drugs was conducted in animals which, if not anesthetized, remained passive and thus did not recruit the neurotransmitter system of interest (eg, Hatip-Al-Khatib *et al*, 2004; Li *et al*, 2006; Shearman *et al*, 2006; Tzavara *et al*, 2006). However, the significance of effects on basal release is not well understood and, as will be illustrated later, effects on basal release may not generalize to effects on an activated system. Depending on the individual neurotransmitter system, basal release of neurotransmitters from resting neurons appears to be largely regulated by the cellular mechanisms controlling synaptic vesicle fusion (Lou *et al*, 2005) and/or reflect non-neuronal sources of neurotransmitter (Xi *et al*, 2003). Furthermore, separate pools of vesicles support basal *vs* activated release (Sara *et al*, 2005), and evidence indicates that basal and evoked release in a particular brain region may be differentially regulated by afferent projection systems (Ahn and Phillips, 2003).

Drugs may increase neurotransmitter release from basal levels by a wide range of the following mechanisms: by depolarizing neurons via local or long-loop mechanisms; by activating presynaptic intracellular mechanisms controlling the selection of vesicles for fusing and/or the rate of vesicle fusion; by influencing release from non-vesicular release pools; or by modulating the activity of afferent projections controlling basal release. It is likely, therefore, that effects on basal release and on activated release are based on essentially different cellular mechanisms. Consequently, effects on basal release do not necessarily inform about the effects of psychopharmacological agents on neurotransmitter release measured in interaction with behavior/cognition-induced activity in the target system. Numerous examples illustrate this view. For example, the effects of positive and negative GABA modulators (benzodiazepine receptor agonists and inverse agonists) cannot be shown with respect to basal ACh release, but are readily apparent in interaction with activated release. In these studies, release was activated by presentation of an attention- and arousal-induced conditioned stimulus

(Sarter and Bruno, 1994). Likewise, the effects of manipulations of the glutamatergic regulation of basal forebrain cholinergic neurons are a function of the state of activity of these neurons (Fadel *et al*, 2001). Laplante *et al* (2004) tested the effects of dopaminergic ligands on prefrontal ACh release in animals with neonatal hippocampal lesions. They observed that administration of dopamine D2 receptor antagonists did not affect release unless assessed in interaction with a stressor (Laplante *et al*, 2004). Similarly, we found that effects of D2 antagonists following systemic or intra-accumbens administration can only be demonstrated following the administration of a pharmacological stressor (Moore *et al*, 1999).

Additional examples further substantiate the dissociation between effects on basal *vs* activated release with respect to other neurotransmitter systems. For example, chronic treatment with the selective serotonin uptake inhibitor paroxetine did not affect basal serotonin release in the hippocampus of rats bred for high *vs* low anxiety-related behavior (HAB, LAB). However, this treatment produced increases in stress-induced release only in HAB rats (Keck *et al*, 2005). Infusions of lidocaine into the central *vs* basalolateral amygdala produced dissociated effects on basal *vs* feeding evoked dopamine release in mesolimbic terminal regions (Ahn and Phillips, 2003).

Although effects on basal neurotransmitter release have been consistently interpreted in terms of indicating the neuronal mechanisms responsible for the behavioral and cognitive effects of a particular drug (Shearman *et al*, 2006), the general finding that drug effects on activated release differ qualitatively from effects on basal release suggests profound limitations of such interpretation. More generally, the functional significance of neurotransmitter dysregulation is likely to manifest mainly in interaction with recruitment of the system of interest, and thus drug effects on resting neurotransmitter systems may be of little relevance for understanding the mechanisms responsible for their potential therapeutic effects. To further illustrate this point, consider a drug thought to alleviate the cognitive symptoms of a disorder by enhancing cholinergic neurotransmission. Ideally, such a drug should act exclusively in interaction with recruitment of the neuronal system mediating cognitive processes. It is indeed difficult to conceive of the functional significance, for example, of an increase in the release of ACh by several hundred percent, whereas the subject is anesthetized or remains in a passive state. Likewise, the measurement of neurotransmitter release or neurotransmitter levels in patients or animal models without challenging the system of interest may yield little information about the degree of dysregulation and its functional significance, or it may fail to reveal such dysregulation altogether.

NEUROTRANSMITTER DYSREGULATION IN RECRUITED CIRCUITS: THE SIGNIFICANCE OF RECRUITMENT MODES

The discussion above stressed the fundamental importance of assessing hypotheses about neurotransmitter dysregulation, or the effects of therapeutic drugs on neurotransmitter levels, in interaction with increased activity of the neuronal system of interest, as opposed to basal release. Moreover, there is accumulating evidence indicating that the type of activation, or the behavioral/cognitive activity 'employed' to recruit the neurotransmitter system determines, not just quantitatively but fundamentally, the effects of drugs on release. Two main examples serve to illustrate this point. The blockade of ionotropic glutamate receptors situated in the region containing the cell bodies of the cholinergic neurons projecting to the cortex produced little effect on basal cortical ACh release but, as would be expected, attenuated the increases in release that are normally produced by a simple conditioned cue eliciting behavioral activation and orientation (Fadel *et al*, 2001). Contrasting effects on release were found in animals performing a task, which taxes attentional functions and is known to depend on the integrity and activity of the cortical cholinergic input system (Arnold *et al*, 2002; McGaughy *et al*, 1996). Specifically, in task-performing animals, blockade of these same ionotropic glutamate receptors resulted in the *augmentation* of the increases in transmitter release normally observed as a function of task performance (Kozak *et al*, 2006a). Thus, the effects of the pharmacological manipulation on neurotransmitter release were diametrically different depending on the stimulus (general activational stimulus *vs* task performance) employed to recruit the neurotransmitter system. These 'paradoxical' increases in transmitter release observed in task-performing animals occurred as the animals' performance declined, stabilized, and recovered following the pharmacological blockade of glutamate receptors. Therefore, these increases in neurotransmitter release were interpreted as mediating the increases in attentional effort that were triggered by the drug-induced impairments in performance and the animals' elevated motivation to regain task control (for a definition of 'attentional effort' and more discussion, see Sarter *et al* (2006)).

The second example concerns the state of neurotransmitter release in an animal model of schizophrenia. The neuronal and cognitive effects of repeated administration of psychostimulants model the important aspects of schizophrenia (eg, Castner and Goldman-Rakic, 2003; Fletcher *et al*, 2005; Laruelle, 2000; Lieberman *et al*, 1997; Martinez *et al*, 2005; Robinson and Becker, 1986; Sarter *et al*, 2005; Segal *et al*, 1981; Tenn *et al*, 2003). Therefore, cortical ACh release was measured, using microdialysis, in animals performing an attentional task, following repeated exposure to amphetamine or vehicle, and subsequent amphetamine challenge. The main finding indicates that in task-performing animals with no previous amphetamine exposure, acute amphetamine administration further increased performance-associated levels of neurotransmitter release. In contrast, in animals with prior amphetamine exposure, the acute challenge caused a striking return of neurotransmitter release to baseline levels and, thereby, the loss of cognitive control of task performance. Importantly, in non-performing animals, such disruption of the regulation of the neurotransmitter systems, as a result of prior amphetamine exposure, was not observed (Kozak *et al*, 2006b). These data indicate that, as a result of prior psychostimulant exposure, a fundamental re-regulation of the target neuronal system and associated circuitry radically alters the effects of subsequent psychostimulant exposure, and that it requires performance-induced activation of the target system and

associated circuits to reveal such re-regulation. Repeated psychostimulant exposure may have modified the regulation of cortical ACh release via altered prefrontal regulation of circuits linking mesolimbic with basal forebrain cholinergic neurons (Neigh-McCandless *et al*, 2002; Neigh *et al*, 2001, 2004). Importantly, the functional impact of this dysregulation is only revealed in interaction with the activation of distributed circuits by task performance (see also Sarter and Bruno, 2000).

These findings have major implications for research on neurotransmitter dysregulation in neuropsychiatric disorders and for the development of therapeutic drugs designed to normalize or counteract abnormal neurotransmitter levels. This evidence suggests that the degree and direction of neurotransmitter dysregulation observed in animal models, or in following psychopharmacological manipulations, depend not just on the level of activity in the neurotransmitter target system (basal *vs* activated), but on the type of the stimulus or the behavioral and cognitive context recruiting the neuronal system of interest (see also Rex *et al*, 2005). Thus, to determine the extent of neurotransmitter dsyregulation, and to begin characterizing the functional significance of such dysregulation, it appears relevant to assess such dysregulation in interaction with behavioral and cognitive activities that depend on the integrity and activity of the target system.

IMPACT ON THE DEVELOPMENT OF PHARMACOTHERAPEUTICS

The significance of the nature of hypotheses about dysregulated neurotransmission (static *vs* dynamic) for the rationales underlying the development of pharmacological treatments can be readily exemplified in the context of evidence indicating unexpectedly dynamic and transient components of release by a major neuromodulator. Measuring ACh release at a sub-second resolution in animals performing a task that requires the detection of behaviorally significant stimuli, we found that increases in cortical cholinergic neurotransmission consists of stimulus-evoked transient (or phasic) as well as slow, or tonic, changes initiated by task onset. (Note that the terms 'phasic and tonic', in this context, refer specifically to the temporal scale of these components of neurotransmitter release and, therefore, should not be confused with the use of these terms by Grace and co- workers on dopamine release, as discussed above). These experiments employed enzyme-selective microelectrodes that permit the real-time monitoring of the release of the neurotransmitter (for technical details, see Parikh *et al*, 2004; Parikh and Sarter, 2006). Recording from the prefrontal cortex of animals performing a cued appetitive response task, cues that evoked disengagement from ongoing behavior and orientation to and monitoring of the food ports ('cue detection') evoked a brief, transient, or phasic, cholinergic signal. In contrast, missed cues did not evoke such signals, and such signals were not observed in a cortical control region (motor cortex). In addition, and beginning with the onset of the behavioral session, slow or tonic changes in cholinergic activity were observed in both cortical regions. The cue-evoked phasic signals observed in the prefrontal cortex were superimposed over these tonic changes (Parikh *et al*, 2006). Collectively, these findings indicate two separate modes of cholinergic neurotransmission.

This finding is of obvious significance for hypotheses focusing on the role of abnormal regulation of cholinergic systems for the development of behavioral and cognitive symptoms, and for drug development therapies focusing on the restoration or modulation of cholinergic neurotransmission. As already mentioned, abnormal levels of ACh release have been hypothesized to contribute to the development of cognitive impairments. As cholinesterase inhibitors continue to be developed for the cognitive symptoms of various disorders (Cummings *et al*, 2006; Koontz and Baskys, 2005), it is evident that the discussion of the rationale underlying this particular pharmacological approach remains incomplete in the absence of evidence indicating the effects of such drugs on both components (phasic/tonic) of cholinergic neurotransmission. Indeed, the relatively limited efficacy of acetylcholinesterase inhibitors in benefiting the cognitive symptoms of patients (Sharma *et al*, 2006) may be due in part to a predominant increase in tonic levels of cholinergic activity. As a result of tonically increased levels of extracellular ACh, elevated presynaptic autoreceptor stimulation would be expected to reduce *de novo* synthesis of ACh (Bertrand and Beley, 1990) and may, therefore, also dampen the generation of phasic increases in cholinergic activity. As such phasic activity is hypothesized to mediate fundamental cognitive operations, it is conceivable that the mixed beneficial and detrimental effects of these drugs on the tonic and phasic components of neurotransmitter release underlie their limited clinical usefulness. The characterization of the modulatory effects of potential therapeutics on both the phasic and tonic changes in cholinergic neurotransmission appears key to understanding the mechanisms underlying the differential pro-cognitive activity of cholinomimetic compounds.

In the absence of evidence defining the mechanisms controlling phasic and tonic aspects of neurotransmission, the definition of neuronal mechanisms that could serve as targets for drug development research poses a challenge. However, drugs modulating transporter capacity, including aspects of transporter expression and trafficking (Sarter and Parikh, 2005), or other presynaptic steps in the regulation of neurotransmitter synthesis and release, may be expected to differentially modulate the phasic and tonic components of neurotransmitter release. Furthermore, the administration of nAChR agonists was found to selectively augment the cue-evoked transient increases in cholinergic activity, and this effect may involve local (prefrontal) glutamate release and AMPA receptor stimulation (Man *et al*, 2006). Thus, it can be speculated that various mechanisms, acting via local and likely multi-synaptic circuits, are capable of modulating differential aspects of neurotransmission. Finally, if evidence for differential afferent regulation of phasic *vs* tonic neurotransmitter, already hypothesized to control phasic *vs* tonic dopamine release in the mesolimbic system (references above), generalizes to other neuromodulator systems, new targets for treatment mechanisms could readily emerge. However, and to reiterate, experiments designed to reveal such afferent target mechanisms likely require activation of relevant circuits, primarily by behavioral/cognitive performance that recruits the circuits of interest.

Although these considerations remain necessarily speculative (for additional discussion of drug finding strategies, see also Sarter, 2006), they illustrate the significance and impact of hypotheses describing abnormal neurotransmission in terms that go beyond steady-state decreases or increases in neurotransmitter release levels or extracellular concentrations, and thus capture the dynamic regulation of multiple components of neurotransmission.

CONCLUSIONS

The aim of this review is to raise an awareness of the theoretical and practical implications of the degree to which neurochemical hypotheses of the behavioral and cognitive symptoms of neuropsychiatric and neurodegenerative disorders capture the dynamic characteristics of neurotransmission. As we pointed out, traditional hypotheses describing static increases or decreases in levels of neurotransmission have been fostered in part by the nature of evidence generated by conventional methods employed to assess the state of neurotransmitter functions in patients and animal models. Furthermore, the widespread practice of measuring neurotransmitter release from neuronal systems that are not recruited by relevant behavioral and cognitive processes has generated evidence that further favors theories describing static neurotransmitter abnormalities and/or failed to reveal the severity and range of such abnormalities.

Recent advances in the development of new methods for monitoring neurotransmitter release at high temporal and spatial resolution (Venton and Wightman, 2003; Kulagina and Michael, 2003; Burmeister *et al*, 2000, 2002, 2006; Parikh *et al*, 2004, 2006; Parikh and Sarter, 2006; Bruno *et al*, 2006a, b; Dale *et al*, 2005; Day *et al*, 2006) assist in revealing the multiple and highly dynamic modes of neurotransmitter release. Furthermore, recent experiments provide stark support for the importance of the view that the demonstration and the nature of abnormal neurotransmitter release in animal models of neuropsychiatric disorders requires experiments examining neurotransmitter systems of interest, whereas they are being challenged by relevant behavioral or cognitive functions (references above). Likewise, as the effects of putative or actual therapeutic drugs on neurotransmitter release represent a crucial component of drug development efforts (eg, Li *et al*, 2006), experiments designed to measure drug effects on activated release, combined with the use of methods revealing effects on different modes of neurotransmission, are likely to reveal more sophisticated and productive neuropharmacological strategies for the development of treatments. For example, although nicotine and other nAChR agonists appear to benefit the cognitive symptoms of schizophrenia, ADHD, and other disorders (eg, Martin *et al*, 2004; Wilens *et al*, 2006), the exact mechanisms underlying these effects have remained unclear. We observed that nicotine selectively augments a transient cholinergic signal in the prefrontal cortex that is evoked by the attentional processing of a stimulus, suggesting that the modulation of a dynamic aspect of neurotransmission, revealed in task-performing animals, may serve as a highly specific target mechanism for drug development (Man *et al*, 2006). Likewise, evidence that phasic dopamine signals in mesolimbic regions mediate distinct aspects of behavior (eg, Di Ciano *et al*, 1998; Montague *et al*, 2004; Stuber *et al*, 2005a, b; Weissenborn *et al*, 1996) not only indicates the limitations of unitary 'dopamine hypotheses', but also suggests that understanding the therapeutic potential of dopaminergic drugs requires insights into drug-induced modulation of the multiple components of evoked dopamine release.

Abnormalities in neurotransmission indicate disruption in neuronal information processing, and thus represent essential aspects of theories of the neuronal mechanisms mediating behavioral and cognitive disorders (eg, Askland and Parsons, 2006; Kornhuber *et al*, 2004). It is expected that evidence from experiments, designed to monitor the multiple modes of neurotransmission *in vivo*, and in interaction with variations of the level and type of recruitment of the neuronal system of interest, is expected to replace conventional, static theories by describing the dynamic, compartmentalized, and recruitment-dependent alterations of multiple components of neurotransmission, and thereby to define more useful and productive treatment targets.

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