

# Possible contributions of a novel form of synaptic plasticity in *Aplysia* to reward, memory, and their dysfunctions in mammalian brain

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Recent studies in *Aplysia* have identified a new variation of synaptic plasticity in which modulatory transmitters enhance spontaneous release of glutamate, which then acts on postsynaptic receptors to recruit mechanisms of intermediate- and long-term plasticity. In this review I suggest the hypothesis that similar plasticity occurs in mammals, where it may contribute to reward, memory, and their dysfunctions in several psychiatric disorders. In *Aplysia*, spontaneous release is enhanced by activation of presynaptic serotonin receptors, but presynaptic D1 dopamine receptors or nicotinic acetylcholine receptors could play a similar role in mammals. Those receptors enhance spontaneous release of glutamate in hippocampus, entorhinal cortex, prefrontal cortex, ventral tegmental area, and nucleus accumbens. In all of those brain areas, glutamate can activate postsynaptic receptors to elevate  $\text{Ca}^{2+}$  and engage mechanisms of early-phase long-term potentiation (LTP), including AMPA receptor insertion, and of late-phase LTP, including protein synthesis and growth. Thus, presynaptic receptors and spontaneous release may contribute to postsynaptic mechanisms of plasticity in brain regions involved in reward and memory, and could play roles in disorders that affect plasticity in those regions, including addiction, Alzheimer's disease, schizophrenia, and attention deficit hyperactivity disorder (ADHD).

Synaptic plasticity has traditionally been divided along three dimensions: (1) modulatory vs. activity-dependent forms, (2) pre- vs. postsynaptic forms, and (3) short- vs. long-term forms. In addition, these basic types of plasticity can be combined in various ways to make hybrids with different functional characteristics (Bailey et al. 2000; Antonov et al. 2003; Cassenaer and Laurent 2012; Huang et al. 2012). For example, modulatory transmitters can act on presynaptic receptors to enhance short-term plasticity (such as post-tetanic potentiation [PTP]) of the evoked release of glutamate, leading to greater recruitment of postsynaptic mechanisms and greater long-term plasticity (Puzzo et al. 2008). Recent studies in *Aplysia* (Jin et al. 2012a,b) have identified a new variation on this theme in which modulatory transmitters enhance spontaneous release of glutamate, which then acts on postsynaptic receptors to recruit mechanisms of intermediate- and long-term plasticity (Fig. 1A). This combination thus links presynaptic modulatory effects with postsynaptic mechanisms of “activity-dependent” plasticity in the absence of activity, and provides a new function for spontaneous release. Because of the novelty of these ideas this review focuses on spontaneous release, which in most of the studies cited was measured in the absence of presynaptic action potentials. However, as illustrated above, modulatory enhancement of presynaptic firing or evoked release can also lead to enhanced activation of glutamate receptors and recruitment of postsynaptic mechanisms of plasticity, so that many of the same arguments might apply.

The simplicity of the *Aplysia* system was important for the discovery of this type of plasticity, but in this review I suggest the hypothesis that similar plasticity occurs in mammals, where it may contribute to reward, memory, and their dysfunctions in disorders including addiction, Alzheimer's disease, schizophre-

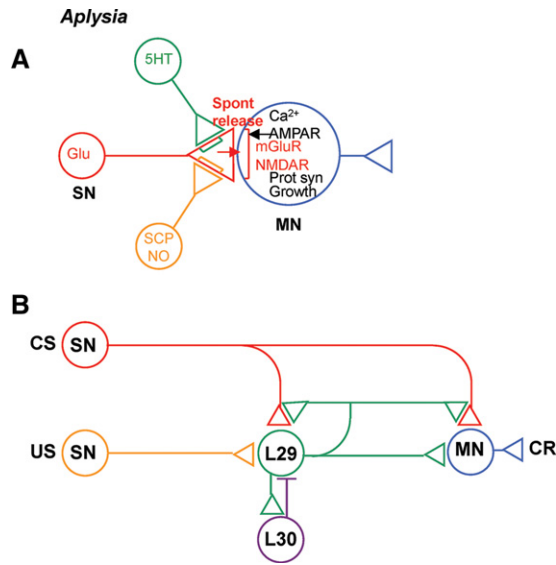
nia, and attention deficit hyperactivity disorder (ADHD). These proposals are not meant to challenge the importance of other, better established mechanisms, which might play complementary roles or act cooperatively with the mechanisms described here.

In *Aplysia*, serotonin (5HT) acts on presynaptic receptors to produce an increase in spontaneous release of glutamate at sensory–motor neuron synapses. This increase is normally mediated by phospholipase C and protein kinase C (PKC), but it can also be produced by adenylyl cyclase and cAMP-dependent protein kinase (PKA) (Braha et al. 1990; Ghirardi et al. 1992; Jin et al. 2012a). The glutamate activates postsynaptic metabotropic glutamate (mGlu) receptors linked to the production of inositol triphosphate (IP<sub>3</sub>), leading to an increase in  $\text{Ca}^{2+}$  and protein synthesis-dependent intermediate-term facilitation. Many of the same postsynaptic mechanisms are recruited during an activity-dependent form of homosynaptic potentiation at these synapses (Jin and Hawkins 2003; Jin et al. 2011a). Intermediate-term facilitation is also accompanied by membrane insertion and an increase in the number of clusters of  $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA)-like glutamate receptors, which precedes increases in clusters of presynaptic proteins and presynaptic varicosities, and therefore could be an early step in synaptic growth during long-term facilitation. Consistent with that idea, spontaneous transmitter release is also required for the induction of long-term facilitation.

Recent studies in several species have shown that spontaneous release also contributes to other synaptic effects, including some cases of homeostatic scaling (Sutton et al. 2004, 2006, 2007; Frank et al. 2006, 2009; Dickman and Davis 2009; Zhang et al. 2009; Lee et al. 2010; Nosyreva et al. 2013). Scaling in those cases has additional similarities to intermediate- and long-term facilitation in *Aplysia*: Both types of plasticity can involve postsynaptic  $\text{Ca}^{2+}$ , protein synthesis, AMPA receptor insertion, and modulation of the presynaptic probability of release. However, scaling has an opposite sign of action compared to facilitation (during

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Article is online at <http://www.learnmem.org/cgi/doi/10.1101/lm.031237.113>.



**Figure 1.** Novel synaptic (A) and circuit (B) mechanisms in *Aplysia* that are involved in learning and memory. (SN) Sensory neuron, (MN) motor neuron, (CS) conditioned stimulus, (US) unconditioned stimulus, (CR) conditioned response, (Glu) glutamate (red), (5HT) serotonin (green), (SCP) small cardioactive peptide, (NO) nitric oxide.

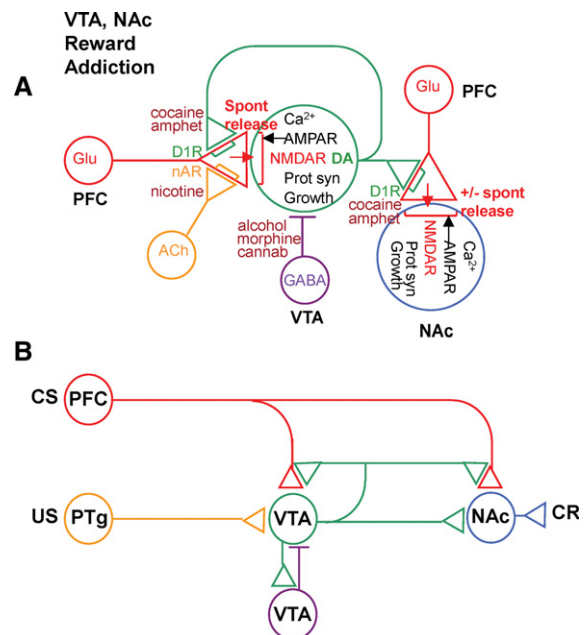
scaling, spontaneous release acts to decrease protein synthesis and synaptic strength). One possible explanation is that a brief, large increase in spontaneous release and, consequently, postsynaptic  $Ca^{2+}$  produces facilitation, whereas a long, small increase produces scaling, similar to the patterns that produce long-term potentiation (LTP) and long-term depression (LTD) (Bear and Malenka 1994). Consistent with that idea, reducing background spontaneous release also tends to increase the evoked EPSP in *Aplysia*, suggesting that scaling and facilitation coexist at the same synapses (Jin et al. 2012a).

In *Aplysia*, spontaneous release is enhanced by activation of presynaptic 5HT receptors. This can also occur in mammals (Cui et al. 2012), but presynaptic D1 dopamine (DA) receptors or nicotinic acetylcholine receptors (nAChR) could play a similar role as well. Presynaptic D1 or nicotinic receptors are present on glutamatergic afferents to hippocampus, entorhinal cortex (EC), prefrontal cortex (PFC), and nucleus accumbens (NAc), as well as afferents to ventral tegmental area (VTA) dopaminergic neurons themselves (Bergson et al. 1995; Jones and Wonnacott 2004; Paspalas and Goldman-Rakic 2005; Dumartin et al. 2007). The D1 receptors act through adenylyl cyclase and PKA to enhance spontaneous release of glutamate in hippocampus, EC, PFC, NAc, and VTA (Kalivas and Duffy 1995; Bouron and Reuter 1999; Yang 1999; Wang et al. 2002, 2012). Results in NAc are mixed, and in some cases presynaptic D1 receptors instead decrease glutamatergic transmission (Nicola and Malenka 1998). Although nicotinic and D1 receptors act through very different molecular mechanisms (see the section on “Synapse-specific effects”), activation of presynaptic nicotinic receptors has the same functional outcome of enhancing spontaneous release of glutamate in hippocampus, EC, PFC, VTA, and other areas (Radcliffe and Dani 1998; Radcliffe et al. 1999; Mansvelder and McGehee 2000; Sharma and Vijayaraghavan 2003; Wang et al. 2006; Tu et al. 2009; Garduño et al. 2012). In many of these studies spontaneous release was used as an indicator of presynaptic or postsynaptic changes, but it could also recruit those changes as it does in *Aplysia*.

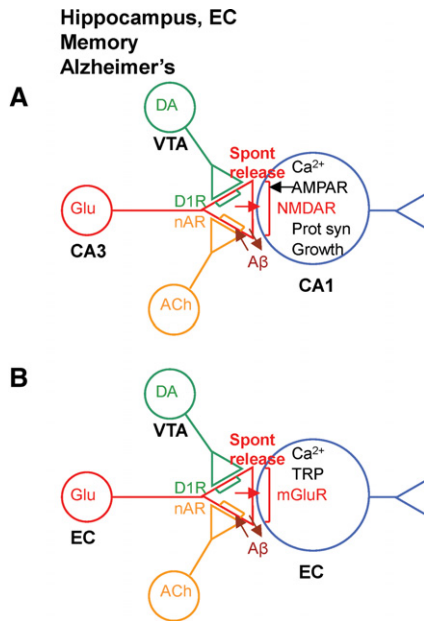
In all of those brain areas, glutamate can activate postsynaptic NMDA receptors (in addition to or instead of metabotropic glu-

tamate receptors, as in *Aplysia*) to elevate  $Ca^{2+}$  and engage mechanisms of early-phase long-term potentiation (E-LTP) including AMPA receptor insertion (Otmakhova and Lisman 1996; Gurden et al. 2000; Mansvelder and McGehee 2000; Huang et al. 2004; Kauer and Malenka 2007; Brown et al. 2010; Luscher and Malenka 2011) and of late-phase LTP (L-LTP) including protein synthesis and growth (Figs. 2A, 3, 4; Huang and Kandel 1995; Hyman et al. 2006; Lemon and Manahan-Vaughan 2006; Navakkode et al. 2007; Bailey et al. 2008). Spontaneous EPSPs are often thought to be insufficient to activate NMDA receptors, but there is growing evidence that they can even at rest (Sutton et al. 2006, 2007; Espinosa and Kavalali 2009; Autry et al. 2011; Povysheva and Johnson 2012; Nosyreva et al. 2013). Furthermore, when spontaneous release is enhanced by a modulatory transmitter, in some cases the EPSPs can summate enough in the postsynaptic dendrites to reach threshold for firing (e.g., Sharma and Vijayaraghavan 2003). Even if the postsynaptic depolarization is subthreshold for firing, it can still be sufficient to further activate NMDA receptors and increase  $Ca^{2+}$  in the spines or dendrites, which is a key event in the induction of plasticity.

Synaptic plasticity in VTA, NAc, and PFC is thought to be involved in reward, plasticity in hippocampus and EC is thought to be involved in reference memory, and plasticity in PFC and EC is thought to be involved in working memory (Goldman-Rakic 1995; Morris et al. 2003; Goldman-Rakic et al. 2004; Hyman et al. 2006; Moser et al. 2008). Thus, presynaptic receptors and spontaneous release may contribute to different aspects of learning-related synaptic plasticity in several brain regions, and could be involved in disorders that affect synaptic plasticity in those regions, including addiction (Kalivas and Duffy 1995; Mansvelder and McGehee 2000; Li et al. 2008; Xiao et al. 2009), Alzheimer’s disease (Welsby et al. 2007; Nimmrich et al. 2008; Puzzo et al. 2008; Khan et al. 2010), schizophrenia (Chen and Yang 2002; Radek et al. 2010), and ADHD (Arnsten 2009). This



**Figure 2.** Novel synaptic (A) and circuit (B) mechanisms in ventral tegmental area (VTA) and nucleus accumbens (NAc) that could be involved in reward and its dysfunction in addiction. (PFC) Prefrontal cortex, (PTg) pedunculoopontine tegmentum, (DA) dopamine (green), (ACh) acetylcholine (yellow), (D1R) D1 dopamine receptor, (nAR) nicotinic acetylcholine receptor.



**Figure 3.** Novel synaptic (A) and intrinsic (B) mechanisms in hippocampus and entorhinal cortex (EC) that could be involved in reference memory, working memory, and their dysfunction in Alzheimer's disease. (TRP) Transient receptor potential.

review summarizes some of the positive evidence in each case to illustrate the plausibility of these ideas, and is not meant to be a comprehensive survey of the literature.

### Reward and addiction

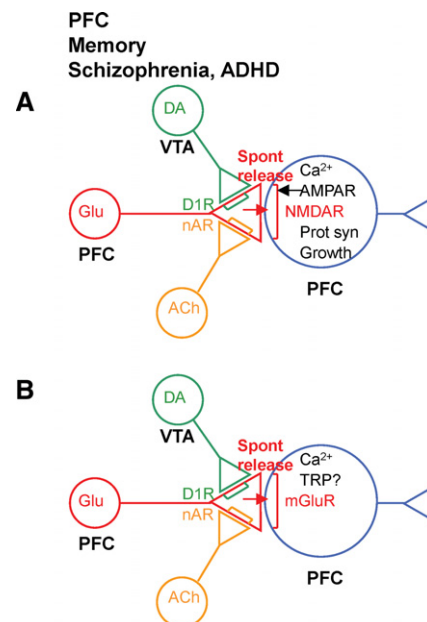
#### *Aplysia* plasticity and circuitry can account for behavioral features of learning

In *Aplysia* the mechanisms of synaptic plasticity described above are embedded in a simple neural circuit (Fig. 1B; Hawkins 1981; Hawkins et al. 1981, 1983; Hawkins and Schacher 1989). Together with the synaptic properties, this circuit can account for many behavioral features of elementary forms of learning of the gill-and siphon-withdrawal reflex, including habituation, dishabituation, sensitization, and classical conditioning (for review, see Hawkins 1989). During conditioning, a mild conditioned stimulus (CS) to the siphon is temporally paired with a noxious unconditioned stimulus (US) to the tail. This training produces greater enhancement of the conditioned response (CR) of gill and siphon withdrawal than unpaired training or training with the US or CS alone. The CS activates sensory neurons (SNs) that make monosynaptic excitatory connections onto motor neurons (MNs) that mediate the CR. Facilitatory neurons, including a small group of L29 interneurons, also receive excitatory input from the CS as well as the US. Firing of L29 neurons activates presynaptic receptors on the CS SNs, and produces facilitation at all the terminals of those neurons, including ones onto the L29 neurons themselves. The presynaptic facilitation is activity-dependent: That is, it is greater at synapses from active SNs than from inactive SNs. Finally, the L29s receive feed forward and feedback inhibition from a small group of L30 interneurons, which act to shut off firing of the L29s. Thus, as conditioning proceeds the synapses from the CS SNs to the L29s are strengthened, causing increased firing of the L29s during the CS, increased negative feedback from the L30s, and thus decreased firing during the US. These synaptic

and circuit properties embody key elements of a psychological model proposed by Rescorla and Wagner (1972), and thus can account for many higher order features of classical conditioning such as second-order conditioning and blocking (Hawkins 1989). These features of conditioning are thought to have a cognitive flavor, and therefore might form a bridge to more complex forms of learning.

Since these ideas were first formulated, a number of additional properties of synaptic plasticity and circuitry have been discovered that might account for additional features of behavioral learning (for review, see Hawkins et al. 2010). For example, the SN–MN synapses also undergo NMDA-dependent Hebbian potentiation, which is induced by nearly coincident pre- and post-synaptic activity (Lin and Glanzman 1994; Antonov et al. 2003). This happens during conditioning because the US drives the MNs (in part via the L29s, which are also excitatory interneurons) just after the CS drives the SNs. The Hebbian potentiation acts synergistically with activity-dependent presynaptic facilitation to strengthen the SN–MN synapses during conditioning (Murphy and Glanzman 1997; Antonov et al. 2003). This hybrid mechanism combines the synapse specificity of Hebbian potentiation with global instruction by motivationally significant stimuli. Furthermore, individual L29s respond to different stimuli and use different facilitatory transmitters, and therefore may serve as internal representations of different USs (Hawkins and Schacher 1989; Antonov et al. 2007). These additional synaptic and circuit properties could explain additional features of conditioning such as response specificity and post-training US exposure effects (Rescorla 1978).

As outlined above, recent studies have found that the facilitatory transmitter also enhances spontaneous release of glutamate from the SNs. The glutamate then recruits postsynaptic mechanisms of intermediate-term facilitation, and initiates a cascade of pre- and postsynaptic mechanisms that may culminate in synaptic growth during long-term facilitation (Jin et al. 2012a,b).



**Figure 4.** Novel synaptic (A) and intrinsic (B) mechanisms in prefrontal cortex (PFC) that could be involved in working memory and its dysfunction in schizophrenia and attention deficit hyperactivity disorder (ADHD).

## Mammalian plasticity and reward circuitry have many similarities to those in *Aplysia*

Synaptic plasticity and circuitry involved in reward in mammals have many similarities to those in *Aplysia*, potentially providing a mechanistic understanding of important aspects of normal reward function and its dysfunction in addiction and other disorders (Fig. 2A,B).

VTA dopamine (DA) neurons are thought to mediate reward, and are thus analogous to the L29 neurons in *Aplysia* (except that they are generally activated by positive USs). Like the L29 neurons, the VTA DA neurons are not homogenous and may be involved in learning about different types of USs (Lammel et al. 2011, 2012; Navratilova et al. 2012). They receive glutamatergic excitatory input from brain regions that process the CS (e.g., the PFC) and glutamatergic, cholinergic, and peptidergic excitatory input from regions that process the US (e.g., the laterodorsal and pedunculopontine tegmentum [PPTg] and lateral hypothalamus) (Floresco et al. 2003; Aston-Jones et al. 2010; Yeomans 2010; Zellner and Rinaldi 2010; Lammel et al. 2012; Kempadoo et al. 2013). During conditioning, the VTA DA neurons increase their firing to the CS and decrease their firing to the US, so that they fire in expectation of reward (Schultz et al. 1997; Schultz 2011). Their firing is thus thought to encode a reward prediction error, i.e., whether current events are better or worse than expected (Montague et al. 1996, 2004). The VTA DA neurons are also activated by rewarding brain stimulation (Wise 2005), and direct activation of those neurons with optogenetic techniques is rewarding (Tsai et al. 2009; Witten et al. 2011).

The VTA neurons release DA that stimulates presynaptic D1 receptors coupled to adenylyl cyclase on the terminals of the CS (e.g., PFC) neurons, and produces potentiation at synapses of those neurons in several brain areas, including the PFC, the NAc, and the VTA DA neurons themselves. The DA potentiation is PKA and NMDA dependent, and is also activity dependent—i.e., it is greater at synapses from active CS neurons (Gurden et al. 2000; Otani et al. 2003; Huang et al. 2004; Sun et al. 2005). Finally, the VTA DA neurons also send projections to postsynaptic neurons in several brain areas, including the PFC and NAc, and receive feed forward and feedback inhibition from GABA neurons in VTA and NAc (Hyman et al. 2006; Nugent et al. 2007; Barrot et al. 2012; Cohen et al. 2012). These properties of the VTA DA neurons are similar to those of the L29 neurons in *Aplysia*, and therefore might account for many of the same behavioral features of learning and reward. In particular, they might at least partially explain why the VTA DA neurons come to fire in expectation of reward during conditioning, which was initially explained by more abstract mathematical models (Montague et al. 1996, 2004; Schultz et al. 1997). These properties might also explain how firing of the VTA DA neurons helps CS neurons gain control of brain areas involved in the behavioral response (Flagel et al. 2011).

The synaptic properties and simple circuits observed in *Aplysia* (Fig. 1) and mammalian brain (Fig. 2) could account for many additional behavioral features of learning (Hawkins 1989; Hawkins et al. 2010), but they cannot account for some others, including learning about CS–US timing. However, the VTA DA neurons are sensitive to that timing, as demonstrated by a decrease in firing at the expected time of the US when it is omitted (Schultz et al. 1997). The behavior of the DA neurons is thus more similar to that of temporal difference models of learning (Sutton and Barto 1990), and might be explained by neural circuits that embody those models (Suri and Schultz 2001; Kobayashi and Okada 2007). In particular, if neurons that computed a temporal reward prediction signal (that is, increased firing from the time of the CS to the expected time of the US) were inserted in the

CS pathway, the circuit shown in Figure 2B would embody basic elements of the temporal difference model. Such neurons have been found in a variety of brain areas that could be part of the CS pathway, including orbitofrontal cortex and PPTg (Suri and Schultz 2001; Okada et al. 2009).

Like presynaptic DA receptors, activation of presynaptic acetylcholine receptors can produce activity- and NMDA-dependent potentiation at the CS neuron synapses (Mansvelder and McGehee 2000; Welsby et al. 2006, 2007). Those synapses also undergo NMDA-dependent Hebbian potentiation, which is induced by nearly coincident pre- and postsynaptic activity driven by the CS and US, respectively. Furthermore, DA and acetylcholine enhance spontaneous release of glutamate from the CS neurons, which may act on postsynaptic receptors to engage the same mechanisms as Hebbian potentiation. As described below, these additional features of synaptic plasticity could help to explain the actions of drugs of abuse during addiction.

### Synapse-specific effects

By itself, dopaminergic or cholinergic enhancement of release would produce potentiation at most or all synapses, and thus might contribute to nonassociative effects such as sensitization. If, however, dopamine or acetylcholine acts synergistically with presynaptic activity to enhance release, the resultant mechanism would be synapse specific and thus might also contribute to associative effects such as conditioning. For example, dopamine and acetylcholine can enhance not only spontaneous release but also short-term plasticity of evoked release during the CS (Young and Yang 2005; Puzzo et al. 2008), which would lead to greater stimulation of postsynaptic NMDARs and greater potentiation specifically at the CS synapses. Dopamine or acetylcholine might also act synergistically with presynaptic activity to enhance long-term plasticity of release, as 5HT does in *Aplysia* (Schacher et al. 1997; Bailey et al. 2000).

Dopamine and acetylcholine have different presynaptic actions, and therefore might interact with presynaptic activity in different ways, possibly with different functional consequences. The nicotinic acetylcholine receptor (nAChR) is coupled to a  $\text{Ca}^{2+}$  permeable ionophore, so that nAChR activation and presynaptic spike activity may act synergistically to increase presynaptic  $\text{Ca}^{2+}$  (perhaps from intracellular stores [Welsby et al. 2006]) and thus enhance release. Recent studies have found that nAChR activation and presynaptic spike activity do act synergistically to produce LTP when spike activity comes slightly (100 msec) after the nAChR activation (Gu and Yakel 2011; Gu et al. 2012). By contrast, the D1 dopamine receptor is coupled to adenylyl cyclase, some forms of which are also  $\text{Ca}^{2+}$  sensitive, so that D1R activation and  $\text{Ca}^{2+}$  influx during spike activity may act synergistically to increase presynaptic cAMP and thus enhance release. This is the same coincidence detection mechanism that has been described in *Aplysia*, where spike activity shortly (500 msec) before 5HT is optimal for increasing cAMP and enhancing release (Yovell and Abrams 1992; Clark et al. 1994). The optimal timing of D1R activation and spike activity has not yet been investigated, but the prediction is that it should be similar to that of 5HT in *Aplysia*.

It is also not yet known in any preparation whether modulatory transmitters and presynaptic spike activity act synergistically to enhance spontaneous release. Preliminary evidence in *Aplysia* suggests that they do not (Eliot et al. 1994), but those experiments investigated short-term facilitation for which spontaneous release may not play an important role (Antonov et al. 2010; Jin et al. 2011a). Longer lasting forms of plasticity that involve synergistic increases in either presynaptic  $\text{Ca}^{2+}$  or cAMP might also involve synergistic enhancement of spontaneous release.

## Drugs of abuse hijack the normal reward process

Drugs of abuse act directly or indirectly to activate the VTA DA reward system (Fig. 2A). Cocaine and amphetamine act at DA terminals to increase extracellular DA levels, whereas alcohol, morphine, and cannabinoids reduce GABA inhibitory input to the DA neurons, producing increased firing of those neurons (Kauer 2004; Hyman et al. 2006; Nugent et al. 2007; Jalabert et al. 2011; Sulzer 2011; Barrot et al. 2012; Oleson et al. 2012; Daberkow et al. 2013). The DA neurons then release DA both from their terminals in other brain areas and from their own dendrites in VTA. DA is thought to act as a signal that current events are better than expected, and drugs of abuse always produce that signal (whether or not it is true), which may explain why they have an advantage over natural rewards (Hyman et al. 2006; Schultz 2011). All of these drugs act through D1 receptors to produce NMDA-dependent E-LTP and AMPA receptor insertion at glutamatergic synapses onto the VTA DA neurons (Ungless et al. 2001; Saal et al. 2003; Hyman et al. 2006; Kauer and Malenka 2007; Sarti et al. 2007; Brown et al. 2010; Luscher and Malenka 2011). Similarly, nicotine acts through nicotinic acetylcholine receptors to produce NMDA-dependent E-LTP at glutamatergic synapses onto the VTA DA neurons (Grillner and Svensson 2000; Mansvelter and McGehee 2000; Gao et al. 2010; Jin et al. 2011b; Mao et al. 2011). The drugs also produce L-LTP, gene regulation, and synaptic growth in VTA (Licata and Pierce 2003; Hyman et al. 2006; Sarti et al. 2007; Chen et al. 2008; Flatscher-Bader et al. 2008).

NMDA-dependent Hebbian LTP at glutamatergic synapses onto the VTA DA neurons preferentially strengthens synapses from CSs that are temporally paired with the US, allowing them to activate the DA neurons themselves (Kauer and Malenka 2007; Zellner and Ranaldi 2010; Wang et al. 2011). Drugs of abuse can also produce similar potentiation by acting directly or indirectly on the same synapses. This process is thought to be involved in the initial rewarding stages of addiction when, for example, a person or animal learns positive associations with cues (CSs) connected with drug use.

Similar drug-induced plasticity occurs at synapses from the CS to other brain areas as well, with different behavioral consequences. Thus, drugs of abuse can also produce LTP in NAc and PFC (Boudreau and Wolf 2005; Boudreau et al. 2007; Huang et al. 2007; Dobi et al. 2011; Luscher and Malenka 2011; Moussawi et al. 2011; Shen et al. 2011; Pascoli et al. 2012; Gipson et al. 2013a,b). Plasticity in those areas may be involved in the early stages of addiction, such as drug sensitization and learning a behavioral response to the CS, and is also thought to be involved in later stages of addiction, such as compulsion and relapse (Bossert et al. 2011; Li et al. 2011c; Pascoli et al. 2012). However, as with D1 receptor activation (see above), the plasticity in NAc is mixed. For example, glutamatergic synapses in the shell (but not the core) of NAc undergo LTD during the early stages of cocaine withdrawal, followed by LTP during later stages of withdrawal (or with prolonged cocaine treatment) and LTD again during reinstatement (Boudreau et al. 2007; Kourrich et al. 2007; Bowers et al. 2010; Ren et al. 2010; Dobi et al. 2011).

Drugs of abuse also produce regulation of genes related to LTP in NAc, including Fos B, c-fos, NR2B and NR4A, CamKII, and dynorphin (Carlezon et al. 1998; Hyman et al. 2006; Lee et al. 2006; Brown et al. 2011; Malvaez et al. 2011; Damez-Werno et al. 2012; Pitchers et al. 2013; Robison et al. 2013; Rogge et al. 2013). That regulation involves a variety of mechanisms, including activation of CREB and epigenetic changes in histone acetylation and methylation (Carlezon et al. 1998; Brown et al. 2011; Malvaez et al. 2011; Maze et al. 2011; Damez-Werno et al. 2012; Sun et al. 2012; Taniguchi et al. 2012; Rogge et al. 2013). In addi-

tion, drugs of abuse produce synaptic growth and structural changes related to L-LTP in NAc, including increases in dendritic branching, spine density, and spine size (Lee et al. 2006; Ren et al. 2010; Dobi et al. 2011; Shen et al. 2011; Dietz et al. 2012; Dumitriu et al. 2012; Gipson et al. 2013a,b; Pitchers et al. 2013; Robison et al. 2013), as well as increases in pre- and postsynaptic proteins (Subramaniam et al. 2001; Gipson et al. 2013b). The drugs produce the same types of structural changes in PFC as well (Robinson and Kolb 1997, 1999; Robinson et al. 2001; Hamilton et al. 2010; Gourley et al. 2012).

Similar plasticity may also occur in hippocampus, which is thought to process information about the context of drug use. The hippocampus sends indirect projections to VTA and NAc (Vorel et al. 2001; Lisman and Grace 2005; Cooper et al. 2006; Fanselow and Dong 2010; Grace 2010; Luo et al. 2011; Britt et al. 2012; Keleta and Martinez 2012) and plays an important role in context conditioning and reinstatement of drug use by re-exposure to the context (Meyers et al. 2003, 2006; Atkins et al. 2008; Martin-Fardon et al. 2008; Ramirez et al. 2009; Lasseter et al. 2010; Xie et al. 2010). VTA DA neurons, in turn, send projections back to hippocampus, where they are thought to enhance LTP and the formation of long-term memories about context (Fig. 3A; Rossato et al. 2009).

As in other brain areas, in vivo exposure to drugs such as cocaine enhances hippocampal LTP (Thompson et al. 2002, 2004; Del Olmo et al. 2006b; Guan et al. 2009; Perez et al. 2010), gene expression (Freeman et al. 2001; Ary and Szumlanski 2007; Krasnova et al. 2008; Perrotti et al. 2008; Tropea et al. 2008), and synaptic growth (Fole et al. 2011). The drugs also enhance synaptic transmission and/or LTP in vitro, in some cases through activation of D1 receptors (Del Olmo et al. 2006a; Stramiello and Wagner 2010; Swant et al. 2010). Likewise, activation of D1 receptors produces activity- and NMDA-dependent E-LTP and L-LTP in hippocampus (Huang and Kandel 1995; Huang et al. 1996; Otmakhova and Lisman 1996; Bach et al. 1999; Swanson-Park et al. 1999; Yang 1999; Li et al. 2003; Lemon and Manahan-Vaughan 2006; Williams et al. 2006; Navakkode et al. 2007, 2010, 2012; Stramiello and Wagner 2008, 2010), and inhibition or knock out of D1 receptors reduces LTP (Frey et al. 1991; Li et al. 2003; Morris et al. 2003; Ortiz et al. 2010).

## The possible roles of presynaptic receptors and spontaneous release in reward and addiction

A question raised by these results is why the potentiation often depends on both NMDA receptors and either D1 or nACh receptors. One idea is that those receptors are all on the postsynaptic neuron and somehow interact (Kauer and Malenka 2007; Argilli et al. 2008; Sun et al. 2009; Nai et al. 2010; Luscher and Malenka 2011; Mao et al. 2011; McGranahan et al. 2011). However, another possibility is that the D1 or nACh receptors are on presynaptic terminals of glutamatergic neurons, where they enhance spontaneous as well as evoked release of glutamate that then activates postsynaptic NMDA receptors (Figs. 2A, 3A). Thus cocaine, amphetamine, alcohol, morphine, and cannabinoids act directly or indirectly to increase extracellular DA, which acts on presynaptic D1 receptors. Similarly, nicotine acts on presynaptic nACh receptors. According to this idea the D1 or nACh receptors are in series with NMDA receptors, which would explain why both are necessary.

In support of that idea, presynaptic D1 and nACh receptors are found in many brain areas, including VTA, NAc, PFC, and hippocampus. Activation of D1 receptors enhances spontaneous release of glutamate in all of those areas (Kalivas and Duffy 1995; Bouron and Reuter 1999; Yang 1999; Wang et al. 2002, 2012). Cocaine, opiates, and alcohol also act through D1 receptors to

enhance spontaneous and evoked release of glutamate in several brain areas, including VTA (Kalivas and Duffy 1995; Li et al. 2008; Deng et al. 2009; Xiao et al. 2009) and NAc (Pierce et al. 1996; McFarland et al. 2003; Dobi et al. 2011; Moussawi et al. 2011; Wissman et al. 2011; Suska et al. 2013; Suto et al. 2013). Similarly, nicotine acts through nACh receptors to enhance glutamate release in VTA (Mansvelder and McGehee 2000; Nomikos et al. 2000), NAc (Gipson et al. 2013b), PFC (Wang et al. 2006), and hippocampus (Radcliffe and Dani 1998; Radcliffe et al. 1999; Liu et al. 2003; Sharma and Vijayaraghavan 2003). The glutamate could then activate postsynaptic NMDA receptors and engage mechanisms of early- and late-phase LTP. This hypothesis is very parallel to recent results from *Aplysia* (Fig. 1A), is consistent with much of the known mammalian data, and provides a simple explanation for why drug-induced potentiation in mammals depends on both NMDA receptors and D1 or nACh receptors.

However, other mammalian data suggest a postsynaptic action of DA and acetylcholine in VTA. Whether DA and acetylcholine have predominantly presynaptic or postsynaptic actions may depend on differences in the experimental protocols. For example, most of the evidence for presynaptic actions comes from experiments in vivo or on slices from young (P10–P20) animals (Kalivas and Duffy 1995; Mansvelder and McGehee 2000; Nomikos et al. 2000; Li et al. 2008; Deng et al. 2009), whereas most of the evidence for postsynaptic actions comes from experiments on slices from older animals (Argilli et al. 2008; Mao et al. 2011). Furthermore, presynaptic and postsynaptic actions are not mutually exclusive, and both may contribute.

## Memory and Alzheimer's disease

### Presynaptic receptors, spontaneous release, and LTP

Presynaptic receptors and spontaneous release may also play important roles in mechanisms of memory in the hippocampus and entorhinal cortex, and in disruption of those mechanisms in Alzheimer's disease (Fig. 3). LTP in both of those areas is thought to be involved in long-lasting or reference memory (Morris et al. 2003; Moser et al. 2008). Activation of D1 receptors in hippocampus produces an increase in spontaneous release of glutamate and plays an important role in LTP (see above). The D1 receptors involved in LTP have often been thought to be postsynaptic, but they might also be presynaptic. Similarly, activation of nACh receptors in hippocampus and EC produces an increase in spontaneous release of glutamate (Radcliffe and Dani 1998; Radcliffe et al. 1999; Liu et al. 2003; Sharma and Vijayaraghavan 2003) and activity-dependent LTP (Welsby et al. 2006, 2007; Kenney and Gould 2008; Lagostena et al. 2008; Tu et al. 2009; Gu and Yakel 2011; Gu et al. 2012), and blocking nAChRs reduces LTP (Yun et al. 2005). Thus presynaptic nACh receptors and spontaneous release might also contribute to LTP in those areas.

### Interaction between presynaptic nACh receptors and A $\beta$

Alzheimer's disease produces a devastating loss of memory that is thought to be due initially to synaptic dysfunction and later to synaptic and cell loss in hippocampus and EC (Palop and Mucke 2010). At the molecular level, these effects are due in part to toxicity caused by accumulation of  $\beta$  amyloid peptide (A $\beta$ ). A $\beta$  is produced in response to activity and released in part at synaptic terminals (Kamenetz et al. 2003; Cirrito et al. 2005; Bero et al. 2011). A variety of evidence suggests that some of the effects of A $\beta$  are caused by interactions with nACh receptors. A $\beta$  binds to nACh receptors or associated molecules with high affinity (Wang et al. 2000; Small et al. 2007; Khan et al. 2010) and activates nACh receptors expressed in oocytes (Dineley et al. 2002). A $\beta$  production is reduced by blocking nACh receptors, suggesting a pos-

itive feedback loop at synapses (Fig. 3A; Wei et al. 2010). In addition, intracellular accumulation of A $\beta$  in Alzheimer's disease may be due in part to binding of A $\beta$  to nACh receptors and endocytosis (Nagele et al. 2002). Consistent with that idea, A $\beta$  deposition is reduced in the entorhinal cortex of elderly people who smoke (Hellstrom-Lindahl et al. 2004; Court et al. 2005; Buckingham et al. 2009; Shimohama 2009; Srivareerat et al. 2011), perhaps due to competition of A $\beta$  and nicotine for binding to nACh receptors. Thus the interaction of A $\beta$  and nACh receptors may contribute to the pathology of Alzheimer's disease in at least three ways: by modulating release of glutamate, A $\beta$  production, and internalization of A $\beta$ .

At very low (picomolar) concentrations A $\beta$  acts as an agonist at nACh receptors (Khan et al. 2010) and can produce an increase in spontaneous release of glutamate (Abramov et al. 2009) and nAChR-dependent enhancements of both PTP and LTP (Puzzo et al. 2008) in hippocampus. Conversely, LTP is reduced in A $\beta$  deficient animals, and that reduction can be rescued by nicotine (Wang et al. 2010; Puzzo et al. 2011).

At higher (nanomolar) concentrations or longer durations A $\beta$  can produce decreases in synaptic transmission and LTP, and loss of glutamate receptors and spines. A variety of mechanisms have been proposed for these effects, including increased excitation of inhibitory interneurons, LTD of excitatory synapses, and neurotoxicity (Palop and Mucke 2010), each of which may contribute at different times and concentrations. Like the positive effects of A $\beta$ , its negative effects depend on nACh and NMDA receptors (Welsby et al. 2007; Shankar et al. 2008; Dziewczapolski et al. 2009; Wei et al. 2010; Gu and Yakel 2011; Li et al. 2011a,b; Kessels et al. 2013). These results suggest that the negative effects may be due in part to excessive stimulation of nACh receptors and release of glutamate which, like A $\beta$ , can produce potentiation, depression, or toxicity depending on its concentration. Consistent with that idea, the reduction in LTP by A $\beta$  involves many of the same molecular pathways as glutamate-induced neurotoxicity (Wang and Qin 2010; Jo et al. 2011; Li et al. 2011a).

Alternatively, high A $\beta$  can block nACh receptors (Liu et al. 2001; Chen et al. 2006; Srivareerat et al. 2011), and could thus produce reductions in spontaneous release and LTP. Consistent with that idea, nicotine or nACh agonists can "rescue" the deficits in LTP and memory produced by high A $\beta$  (Chen et al. 2006; Welsby et al. 2007; Srivareerat et al. 2011). In either case, however, some of the negative effects of high A $\beta$  would be due to interactions with nACh receptors.

### Presynaptic receptors, spontaneous release, and persistent firing

Patients who develop Alzheimer's disease also have earlier deficits in temporary or working memory, which is thought to involve persistent firing of neurons in EC during the delay interval of a working memory task (Suzuki et al. 1997; Young et al. 1997). Persistent firing could also contribute to the properties of grid cells in EC and the encoding of episodic memories (Hasselmo 2008; Hasselmo and Brandon 2008). Persistent firing of neurons in layers III and V of EC in vitro is due in part to activation of group I metabotropic glutamate (mGlu) receptors linked to the production of IP<sub>3</sub>, increased intracellular Ca<sup>2+</sup>, and modulation of transient receptor potential (TRP) channels (Hasselmo 2008; Yoshida et al. 2008). Similar processes also occur in CA1 pyramidal neurons (El-Hassar et al. 2011). Presynaptic receptors and spontaneous release may play important roles in these effects as well. Thus, activation of presynaptic nACh receptors enhances spontaneous release of glutamate from layer VI to layer V neurons in EC (Tu et al. 2009). As in *Aplysia*, the glutamate could act through group I mGlu receptors to increase postsynaptic Ca<sup>2+</sup> and, in

this case, modulate TRP channels (Fig. 3B). Binding of A $\beta$  to the nACh receptors could interfere with these processes in Alzheimer's disease.

## Working memory, schizophrenia, and ADHD

Similarly, presynaptic receptors and spontaneous release could play an important role in persistent firing in PFC, which is thought to contribute to working memory as well (Goldman-Rakic 1995). Deficits in working memory are among the cognitive symptoms of schizophrenia and ADHD, and presynaptic nACh receptors and D1 dopamine receptors in PFC have been implicated in working memory and its dysfunction in schizophrenia and ADHD (Murphy et al. 1996; Goldman-Rakic et al. 2004; Young et al. 2007; Gamo et al. 2010; Radek et al. 2010). Because less is known about the role of nACh receptors, this review focuses on the possible role of D1 receptors.

Presynaptic D1 receptors are found in PFC (Paspalas and Goldman-Rakic 2005), where they produce a PKA-dependent enhancement of spontaneous release of glutamate (Wang et al. 2002). That enhancement might contribute to persistent firing of PFC neurons in two ways. First, D1 receptors act through PKA to produce activity- and NMDA-dependent E-LTP and L-LTP (Gurden et al. 2000; Otani et al. 2003; Huang et al. 2004; Matsuda et al. 2006), which might contribute to circuit mechanisms of persistent firing at PFC–PFC synapses (Fig. 4A; Paspalas and Goldman-Rakic 2005). Second, D1 receptors also act through PKA and mGlu receptors to modulate channels that contribute to a cell autonomous mechanism of persistent firing (Fig. 4B, Onn and Wang 2005; Witkowski et al. 2008; Sidropoulou et al. 2009). In both cases presynaptic D1 receptors may enhance spontaneous release of glutamate, which then acts on postsynaptic NMDA or mGlu receptors. That effect would be analogous to the effect of presynaptic nACh receptors on persistent firing of neurons in EC (Fig. 3B), or of presynaptic 5HT receptors on postsynaptic mechanisms of facilitation in *Aplysia* (Fig. 1A).

## Conclusions

Recent studies in *Aplysia* suggest that presynaptic receptors and spontaneous release contribute to a new form of synaptic plasticity that links presynaptic modulatory effects to postsynaptic mechanisms of activity-dependent plasticity, in the absence of activity (Jin et al. 2012a,b). This review has summarized evidence suggesting that presynaptic receptors, spontaneous release, and a similar hybrid form of plasticity may also be involved in a variety of functions in different mammalian brain areas, including reward in VTA, NAc, and PFC, reference memory in hippocampus and EC, and working memory in PFC and EC, and also in disorders that affect plasticity in those brain areas, including addiction, Alzheimer's disease, schizophrenia, and ADHD. This novel form of plasticity could thus play widespread and important roles in mammals as well as in *Aplysia*.

This review is highly selective and does not include other transmitter systems, molecular pathways, and brain areas that are also important for these brain functions and disorders. In addition, a number of other, better established types of plasticity no doubt also play important roles. However, the different transmitters, pathways, brain areas, and types of plasticity are not mutually exclusive, and they could play complementary roles or act cooperatively with the mechanisms described here. For example, a large body of evidence indicates that Hebbian LTP (induced by coincident pre- and postsynaptic activity) plays an important role in reward and addiction in VTA (Kauer and Malenka 2007; Zellner and Rinaldi 2010). That mechanism could act cooperatively with the

presynaptic modulatory mechanism described here, just as Hebbian LTP and activity-dependent presynaptic facilitation act cooperatively during conditioning in *Aplysia* (Antonov et al. 2003). Finally, although the evidence presented in this review suggests that these ideas are plausible, at the moment they are still speculative and remain to be tested experimentally. However, in so far as those tests reveal novel mechanisms of plasticity and its disruption in psychiatric disorders, they could also suggest novel treatment strategies.

## Acknowledgments

I thank Ottavio Arancio, Eric Kandel, Christoph Kellendonk, Amir Levine, Eleanor Simpson, and Andrew Teich for their comments. Preparation of this article was supported by grants from the NIH (GM097502, NS083690) and Whitehall Foundation.

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Received March 29, 2013; accepted in revised form June 14, 2013.