

## FEATURE ARTICLE

# Dopamine D1/D5 Receptors Mediate Informational Saliency that Promotes Persistent Hippocampal Long-Term Plasticity

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**Dopamine (DA) plays an essential role in the enablement of cognition. It adds color to experience-dependent information storage, conferring saliency to the memories that result. At the synaptic level, experience-dependent information storage is enabled by synaptic plasticity, and given its importance for memory formation, it is not surprising that DA comprises a key neuromodulator in the enablement of synaptic plasticity, and particularly of plasticity that persists for longer periods of time: Analogous to long-term memory. The hippocampus, that is a critical structure for the synaptic processing of semantic, episodic, spatial, and declarative memories, is specifically affected by DA, with the D1/D5 receptor proving crucial for hippocampus-dependent memory. Furthermore, D1/D5 receptors are pivotal in conferring the properties of novelty and reward to information being processed by the hippocampus. They also facilitate the expression of persistent forms of synaptic plasticity, and given reports that both long-term potentiation and long-term depression encode different aspects of spatial representations, this suggests that D1/D5 receptors can drive the nature and qualitative content of stored information in the hippocampus. In light of these observations, we propose that D1/D5 receptors gate hippocampal long-term plasticity and memory and are pivotal in conferring the properties of novelty and reward to information being processed by the hippocampus.**

**Keywords:** cognition, hippocampus, learning and memory, review, synaptic plasticity

## Introduction

Dopamine (DA) is a neurotransmitter in the central nervous system that belongs to the catecholamines (Carlsson et al. 1962). DA neurons are categorized in dopaminergic systems based on their innervation territories. Four axonal dopaminergic pathways are described: 1) nigrostriatal, 2) mesolimbic, 3) mesocortical, and 4) tuberoinfundibular (Vallone et al. 2000). DA subserves a multitude of roles in cognition-related brain functions: It regulates memory, motivation, mood, motor activity, and neuroendocrine integration (Horn et al. 1979; Fluckiger et al. 1987) and is released after novel (Ljungberg et al. 1992), salient sensory (Ungless 2004), aversive (Bromberg-Martin et al. 2010), or reinforcement-relevant (reward) stimuli (Schultz et al. 1993). For many decades, its role in cognitive disorders and brain disease has been intensely studied. This derived from observations that a strikingly low DA concentration occurs in the basal ganglia of patients with Parkinson's disease (Ehringer and Hornykiewicz 1960) and that DA dysfunctions contribute to cognitive disorders such as schizophrenia (Goto and Grace 2007; Lodge and

Grace 2011), drug addiction (Robinson and Berridge 1993), attention deficit hyperactivity disorder (Del Campo et al. 2011), and possibly Alzheimer's disease (Kumar and Patel 2007; Jürgensen et al. 2011).

Experimental evidence suggests that DA is highly relevant for the modulation of hippocampus-dependent synaptic plasticity and memory (Jay 2003; Lisman and Grace 2005; Lisman et al. 2011). These effects are mediated by 2 distinct groups of DA receptors: The D1/D5 (D1-like) receptors and the D2-like receptors (Tiberi et al. 1991; Vallone et al. 2000; Beaulieu and Gainetdinov 2011) (Fig. 1), whereby, in recent decades, the D1/D5 receptors have received increasing attention. This is because of the significant role that they play in the regulation of both hippocampus-dependent synaptic plasticity (the mechanisms believed to underlie learning) and hippocampus-dependent memory (Huang and Kandel 1995; Lemon and Manahan-Vaughan 2006; Bethus et al. 2010; Clausen et al. 2011; Da Silva et al. 2012). Intriguingly, D1/D5 receptors regulate both forms of persistent (>24 h) synaptic plasticity and appear to contribute importantly to the earmarking of information as novel or salient (Davis et al. 2004; Ungless 2004; Lemon and Manahan-Vaughan 2006, 2011), which in turn strongly influences hippocampus-dependent memory encoding and retention (Adcock et al. 2006). The D2-like receptors, in contrast, seem less significant for hippocampus-dependent information processing, be it at the levels of synaptic plasticity or memory formation (Kulla and Manahan-Vaughan 2003; King et al. 2010). Activation of D1/D5 receptors alter excitability in the hippocampus (Ito and Schumann 2007; Hamilton et al. 2010) and therefore influence the thresholds for the induction of synaptic plasticity or memory encoding. Different hippocampal subregions such as the dentate gyrus (DG), cornu ammonis 1 (CA1) and subiculum that exercise distinct functions in information processing within the hippocampus are also modulated by the activation of D1/D5 receptors (Kulla and Manahan-Vaughan 2000; Lemon and Manahan-Vaughan 2006; Othmakhova and Lisman 1996; Roggenhofer et al. 2010).

Activity-dependent alterations in synaptic strength encode new information in the brain. Two major forms can be distinguished: 1) long-term potentiation (LTP; Bliss and Lomo 1973; Bliss and Collingridge 1993) and 2) long-term depression (LTD) of synaptic strength (Dudek and Bear 1992; Manahan-Vaughan 1997). LTP that is induced solely by electrical afferent stimulation (electrically induced plasticity) was first reported roughly 40 years ago in the DG of the rabbit after high-frequency stimulation (HFS) of the perforant path (Bliss and Lomo 1973). Hippocampal LTD was described

for the first time in Schaffer collateral (SC)–CA1 synapses (Dunwiddie and Lynch 1978) and is electrically induced by low-frequency stimulation (LFS: 1–3 Hz for 5–15 min). Both phenomena are believed to underlie hippocampal learning and memory (Bliss and Collingridge 1993; Bear 1996; Kemp and Manahan-Vaughan 2007). This likelihood is supported by more recent studies that address a phenomenon known as learning-facilitated plasticity. Here, weak electrical afferent stimulation that under control conditions elicits either no change in basal synaptic strength, or elicits short-term plasticity, leads to persistent plasticity if coupled with a novel learning experience (Manahan-Vaughan and Braunewell 1999; Goh and Manahan-Vaughan 2012).

Studies of learning-facilitated plasticity suggest that LTP and LTD are responsible for the encoding of different elements of a memory representation. Thus, LTP is associated with the encoding of global space, spatial change, or contextual fear (Straube et al. 2003; Kemp and Manahan-Vaughan 2004; Whitlock et al. 2006), whereas LTD is associated with the encoding of spatial context (Manahan-Vaughan and Braunewell 1999; Etkin et al. 2006; Kemp and Manahan-Vaughan 2004, 2007, 2008a; Goh and Manahan-Vaughan 2012). The precise contributions of LTP and LTD to spatial representation are tightly linked to the respective hippocampal subregions (Kemp and Manahan-Vaughan 2008a; Hagena and Manahan-Vaughan 2011). What is striking, however, is that D1/D5 receptors regulate both persistent LTP (Huang and Kandel 1995; Lemon and Manahan-Vaughan 2006) and persistent LTD (Lemon and Manahan-Vaughan 2006), suggesting that these receptors exert control over the kind of information contributed by the different forms of synaptic plasticity to memory representations.

LTP has been subdivided into temporal categories referred to as 1) short-term potentiation that typically requires calcium entry through, for example, *N*-methyl-D-aspartate (NMDA) receptors, 2) early (E)-LTP requiring both NMDA receptors and the activation of metabotropic glutamate (mGlu) receptors (Bashir et al. 1993) and protein kinases (Malenka et al. 1989), and to a lesser extent, phosphatases; 3) late (L)-LTP that is based on the expression of early immediate genes (Jones et al. 2001) requires protein translation, and (4) late late (LL)-LTP that requires protein transcription (Nguyen et al. 1994; Villers et al. 2010) and facilitates LTP consolidation (Ryan et al. 2012). Similar delineations are evident for LTD: An early LTD (E)-LTD reliant on the activation of NMDA receptors (at least in the CA1 region; Dudek and Bear 1992; Manahan-Vaughan 1997), mGlu receptors (Manahan-Vaughan 1997), and protein phosphatases (Mulkey et al. 1993), late LTD (L)-LTD that is dependent on gene expression (Abraham et al. 1994) and protein translation (Manahan-Vaughan et al. 2000; Parvez et al. 2010), and late late (LL)-LTD that requires protein transcription (Kauderer and Kandel 2000). Although electrically induced and learning-facilitated plasticity share similarities in their underlying mechanisms (Manahan-Vaughan 1997; Popkirov and Manahan-Vaughan 2011), they also display quite distinct properties. For example, learning-facilitated and not electrically induced persistent plasticity require beta-adrenoreceptors (Kemp and Manahan-Vaughan 2008b), and Madronal et al. (2009) showed that paired-pulse facilitation is differently modulated by electrically induced LTP or changes in synaptic strength evoked by classic eye-blink conditioning (i.e. learning-facilitated plasticity). It is however quite possible that learning-facilitated plasticity is

more sensitive to neuromodulation, and more physiological than plasticity elicited by electrical stimulation alone, which could explain the abovementioned data.

The hippocampus contributes to many behaviors such as anxiety (Engin and Treit 2007), goal-directed behavior (Pennartz et al. 2011), informational processing, olfactory identification, and spatial navigation and orientation (Hölscher 2003). But most strikingly, the different hippocampal subregions are believed to engage in different aspects of creation of a memory trace. Whereas the DG is postulated to engage in pattern separation, whereby similar information is recognized as not being the same, the CA3 region engages in pattern completion, whereby incoming information leads to the complete retrieval of a stored representation, should that information have contributed previously to the creation of a memory (Lee et al. 2004; Goodrich-Hunsaker et al. 2008). The CA1 region is believed to integrate information coming from the other subregions and also participates in mismatch detection (Lisman and Otmakhova 2001). Given this division of labor, it is perhaps not so surprising that the D1/D5 receptors exert a differential influence on synaptic plasticity in these structures. Here, it must be however emphasized that the role of these receptors in the CA3 region has not yet been examined.

#### DA Release in the Hippocampus

DA is released from axon terminals residing in the hippocampus (Frey et al. 1990), which originates from midbrain sources with the ventral tegmental area (VTA, A10 cell group in the rat nomenclature), comprising the main source. Release occurs in the hippocampus some minutes after novelty exposure in the hippocampus (Ihalainen et al. 1999). This implies that DA is a key component in enabling processing of novel information in the hippocampus. In temporoammonic (TA) synapses, DA acts over a range of stimulus frequencies (5–100 Hz) as a high-pass filter that enhances responses to high-frequency inputs, while reducing the influence of low-frequency inputs (Ito and Schumann, 2007). Strikingly, LTP at SC–CA1 synapses is unaffected, whereas LTP at TA synapses is enhanced by DA. This suggests that DA increases the relevance of information being passed from the entorhinal cortex via the TA synapses directly to the hippocampus, compared with information being processed “internally” at SC–CA1 synapses, which in turn alters informational content and the nature of information storage by influencing the direction of change in synaptic weights. This may subserve the integration of new information with previously encoded information as it exits the hippocampus.

The VTA is not the only source of DA for the hippocampus. Aside from the VTA, the hippocampus receives inputs from the retrorubral area A8 and the substantia nigra pars compacta A9 (Beckstead et al. 1979) and interacts with other dopaminergic nuclei such as the nucleus accumbens (NAcc; Figs 2 and 3). For example, mesocortical DA projections from the VTA to the prefrontal cortex (PFC) may play a critical role in modulating information processing by hippocampus–PFC interactions (Seamans et al. 1998; Goto and Grace 2008a). In addition, although it does not project directly to the hippocampus, the NAcc (together with the ventral pallidum, VP) serves as the downward arm of the hippocampal–VTA loop, serving to help combine the novelty signal with salience and goal information (Lisman and Grace 2005; Figs 2 and 3). In

addition to its main role in gating limbic and cortical inputs, the NAcc is involved in improving goal-directed behavior (Gruber et al. 2009) and in enabling hippocampal-dependent spatial information to gain control over appetitive learning (Ito and Hayen 2011). The role of the NAcc in informational gating has been reviewed elsewhere in great detail (Grace et al. 2007; Goto and Grace 2008b; Yin et al. 2008).

Taken together, the known role of the dopaminergic nuclei that impinge on the hippocampus supports that DA is released by novelty and reward-related experience and that this information enables the hippocampus to add meaning to the information it processes. By this means, salience is conferred to information stored. The relative regulation of LTP and LTD in the different hippocampal subfields is one possible means through which the hippocampus then integrates and encodes this information into a memory engram or spatial representation.

### **Influence of D1/D5 Receptors on LTP in the DG**

The DG is the functional “gateway” to the hippocampus. Mixed effects on electrically induced LTP have been reported after activation of D1/D5 receptors in this structure (Table 1A), but predominantly an inhibition of LTP has been reported following D1/D5 receptor antagonism (Yanagihashi and Ishikawa 1992; Kusuki et al. 1997; Swanson-Park et al. 1999). This suggests that these receptors play a pivotal role in determining whether LTP occurs in the DG in response to incoming stimuli. D1/D5 receptor activation during a “reward” or “novelty” signal has been proposed to increase DG excitability (Hamilton et al. 2010) such that novel sensory information passes the informational gateway and filter of the DG to enter the circuitry of the hippocampal CA3–CA1 region (Heinemann et al. 1992; Hamilton et al. 2010). This in turn may relate to the function of the DG in pattern completion (Kesner et al. 2000).

Information gating in a more global sense is also supported by the DA. This type of gating may enable oscillatory network activity between different brain areas involved in learning (Buzsaki and Draguhn 2004). D1/D5 receptor activation can, for example, modulate theta burst firing in the medial septal/vertical limb of diagonal band neurons that project to the hippocampus (Fitch et al. 2006). Furthermore, DA suppresses cholinergic gamma oscillations in area CA3 via D1 receptor activation (Weiss et al. 2003). It has been suggested that DA in particular alters the frequency firing pattern of neurons (theta and gamma frequency volleys; Ito and Schumann 2007) that have been observed in the entorhinal cortex during exploratory behavior of rodents (Chrobak et al. 2000) thereby changing informational content.

### **Influence of D1/D5 Receptors on LTP in the CA1 Region**

In contrast to the DG, where only L-LTP is affected, in vitro studies of SC–CA1 synapses showed that both E-LTP (Otmakhova and Lisman 1996) and L-LTP (Frey et al. 1991; Huang and Kandel 1995) are prevented or reduced (Swanson-Park et al. 1999) by a D1/D5 antagonist, whereas agonists of D1/D5 receptors lead to enhanced E-LTP (Otmakhova and Lisman 1996). The magnitude of both E- and L-LTP is also markedly reduced in hippocampal slices from D1 receptor –/– mice compared with wild-type mice (Granado et al.

2008). In line with these findings, in vivo studies showed that HFS-induced LTP at SC–CA1 synapses is facilitated by D1/D5 receptor activation in freely behaving rats (Lemon and Manahan-Vaughan 2006; Table 1A). However, D1/D5 receptor antagonism prevents only L-LTP in SC–CA1 synapses (Lemon and Manahan-Vaughan 2006). The differences between the in vitro and in vivo studies may relate to the different kinds of stimulation protocols that were used to elicit LTP of differing robustness and durations.

### **Effect of D1/D5 Receptor Activity on Depotentialization of LTP**

Although it is not a persistent form of synaptic plasticity, depotentialization bears a mention in the context of D1/D5 regulation of hippocampal synaptic plasticity (Table 1C). Depotentialization is an interesting phenomenon that occurs when LFS is applied within a very short time-window (maximum 30 min) of inducing LTP (Staubli and Lynch 1990; Kulla et al. 1999) and has been proposed to comprise a functional correlate of active forgetting or perhaps of learning interference. This form of synaptic plasticity is distinct to LTD, as it does not engage the same phosphorylation/dephosphorylation profile of the  $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (Lee et al. 1998) and has different sensitivities to, for example, mGlu receptor ligands (Manahan-Vaughan 1997; Fitzjohn et al. 1998; Kulla et al. 1999; Kulla and Manahan-Vaughan 2008). Another aspect of depotentialization is the associative regulation of this phenomenon, as exemplified by an in vitro study in rats showing that the synthesis of plasticity-related proteins (PRPs) by L-LTP in one input facilitated E- into L-LTD in another input. Thus, long-term plasticity in one synaptic input is associatively induced by PRPs of another synaptic input, in a process referred to “cross tagging” (Sajikumar and Frey 2004). Associative long-term plasticity and synaptic tagging also seem to be dependent on D1/D5 receptor activation (Sajikumar and Frey 2004).

Interestingly, D1/D5 receptor manipulation affects LFS-induced depotentialization of LTP both in vitro and in vivo (Otmakhova and Lisman 1998; Kulla and Manahan-Vaughan 2000). D1/D5 receptor agonists reduce the depotentialization of LTP by LFS in CA1 and in DG, whereas D1/D5 receptor antagonists inhibit this effect (Kulla and Manahan-Vaughan 2000) presumably via a cyclic 3'5' adenosine monophosphate (cAMP)-dependent mechanism (Otmakhova and Lisman 1998).

If depotentialization comprises forgetting, it suggests that D1/D5 receptor activation can hinder this process. As depotentialization of LTP is a successive process—first LTP is induced and afterwards depotentialization is initiated, it implies that D1/D5 receptor activation can veto a “decision” to forget information that was initially earmarked for long-term storage. Again, this possibility fits well into a role for these receptors in mediating informational salience.

### **Effect of D1/D5 Receptor Activity on Hippocampal LTD**

LTD to some extent is a mirror image of LTP, comprising persistent decreases in synaptic strength that occur following patterned afferent stimulation to the hippocampus. In recent years, it has become apparent that this phenomenon is an information storage mechanism that likely cooperates with LTP to generate spatial and/or memory representations

**Table 1**

D1/D5 receptors and hippocampal synaptic plasticity

Drug/knock out	First application time	Hippocampal region	Plasticity protocol	Effect on plasticity	Duration of effect	References
<b>(A) Effects of DA on hippocampal LTP via D1/D5 receptors</b>						
In vitro electrophysiology						
D1/D5 agonist	Before HFS	CA1	HFS (10 × 100 Hz)	E-LTP↑	40 min	Otmakhova and Lisman (1996)
D1/D5 agonist	Before HFS	CA1	HFS (3 × 100 Hz)	LTP↑	2 h	Swanson-Park et al. (1999)
D1/D5 agonist	Before HFS	SUB	HFS (4 × 100 Hz)	LTP↑	40 min	Roggenhofer et al. (2010)
D1/D5 agonist	After 1 h of baseline	CA1	Test pulses (0.2 Hz)	Slow-onset late-LTP	5 h	Navakodde et al. (2007)
D1/D5 agonist						
D1/D5 antagonist	After HFS	CA1	HFS (3 × 100 Hz)	No effect	3 h	Frey et al. (1991)
D1/D5 antagonist	Before HFS	DG	HFS (3 × 100 Hz)	No effect	>3 h	Swanson-Park et al. (1999)
D1/D5 antagonist	Before HFS	CA1	HFS (10 × 100 Hz)	Early LTP↓	40 min	Otmakhova and Lisman (1996)
D1/D5 antagonist	Before HFS	CA1	HFS (3 × 100 Hz)	LTP↓	>3 h	Swanson-Park et al. (1999)
D1/D5 antagonist	During HFS	CA1	HFS (3 × 100 Hz)	L-LTP ↓	>4 h	Frey et al. (1990)
D1/D5 antagonist	During HFS	CA1	HFS (3 × 100 Hz)	L-LTP ↓	>6 h	Huang and Kandel (1995)
D1/D5 antagonist	During HFS	CA1	HFS (3 × 100 Hz)	L- LTP ↓↓	>2 h	Frey et al. (1991)
D1/D5 antagonist	During HFS	CA1	HFS (21 × 100 Hz)	S1:LTP↓↓	6 h	Navakodde et al. (2010)
				S2: LTP↓↓	6 h	
D (1)−/− mice	−	CA1	HFS (3 × 100 Hz)	E-, L-LTP ↓	6 h	Granado et al. (2008)
D (1) −/− mice	−	CA1	HFS (3 × 100 Hz)	LTP↓	2 h	Matthies et al. (1997)
In vivo electrophysiology						
D1/D5 agonist	Before HFS	DG	HFS (100 p × 100 Hz)	LTP↑	1 h	Kusuki et al. (1997)
D1/D5 agonist	Before HFS	CA1	Spatial novelty	LTP↑	3 h	Li et al. (2003)
D1/D5 agonist	Before HFS	CA1	HFS (4 × 100 Hz)	LTP↑	4 h	Lemon and Manahan-Vaughan (2006)
D1/D5 agonist	Before HFS	DG	HFS (10 × 200 Hz)	No effect	24 h	Kulla and Manahan-Vaughan (2000)
D1/D5 agonist	Before HFS	DG	HFS (10 × 400 Hz)	LTP ↓↓	2 h	Yanagihashi and Ishikawa (1992)
D1/D5 antagonist	Before HFS	DG	HFS (10 × 200 Hz)	No effect	24 h	Kulla and Manahan-Vaughan (2000)
D1/D5 antagonist	Before HFS	DG	HFS (3 × 100 Hz)	No effect	>3 h	Swanson-Park et al. (1999)
D1/D5 antagonist	Before HFS	CA1	HFS (3 × 100 Hz)	LTP ↓↓	>3 h	Swanson-Park et al. (1999)
D1/D5 antagonist	Before HFS	DG	HFS (10 × 100 Hz)	LTP ↓↓	1 h	Kusuki et al. (1997)
D1/D5 antagonist	Before HFS	CA1	HFS (4 × 100 Hz)	L-LTP↓↓	>2 h	Lemon and Manahan-Vaughan (2006)
D1/D5 antagonist	Before HFS	CA1	Empty holeboard	L-LTP↓↓	4 h	Lemon and Manahan-Vaughan (2006)
D1/D5 antagonist	Before HFS	DG	HFS (10 × 400 Hz)	Reversal of inhibited LTP	2 h	Yanagihashi and Ishikawa (1992)
<b>(B) Effects of DA on hippocampal LTD by D1/D5 receptors</b>						
In vitro electrophysiology						
D1/D5 agonist	After LFS	CA1	DHPG	No effect on LTD	2 h	Mockett et al. (2007)
D1/D5 agonist	Before LFS	CA1	LFS (450 × 1 Hz)	LTD↑	40 min	Chen et al. (1995)
D1/D5 agonist	Before LFS	CA1	LFS (450 × 1 Hz)	LTD↑	1 h	Liu et al. (2009)
D1/D5 agonist	After LFS	CA1	LFS (1200 × 3 Hz)	LTD↓	2 h	Mockett et al. (2007)
D1/D5 agonist	After LFS	CA1	NMDA	LTD↓	2 h	Mockett et al. (2007)
D1/D5 antagonist	Before LFS	CA1	LFS (450 × 1 Hz)	LTD↓↓	40 min	Chen et al. (1995)
D1/D5 antagonist	During sLFS	CA1	SLFS (2700 × 1 Hz)	L-LTD↓ (S1 + S2)	7 h	Saikkumar and Frey (2004)
D1/D5 antagonist	30 min after LTD in S1	CA1	SLFS (2700 × 1 Hz)	No effect L-LTD (S1 + S2)	7 h	Saikkumar and Frey (2004)
In vivo electrophysiology						
D1/D5 agonist	Before novel spatial exploration	CA1	Novel spatial exploration, afferent stimulation	LTD	4 h	Lemon and Manahan-Vaughan (2011)
D1/D5 agonist	Before HFS	CA1	HFS (2 × 100 Hz) of LC	E- into L-LTD↑	24 h	Lemon and Manahan-Vaughan (2011)
D1/D5 agonist	Before HFS	CA1	LFS (600 × 1 Hz)	LTD↑	4 h	Lemon and Manahan-Vaughan (2006)
D1/D5 antagonist	Before HFS	CA1	LFS (900 × 1 Hz)	LTD↓	4 h	Lemon and Manahan-Vaughan (2006)
D1/D5 antagonist	Before HFS	CA1	Novel spatial exploration	L-LTD↓	4 h	Lemon and Manahan-Vaughan (2006)
D1/D5 antagonist	Before HFS	CA1	HFS (2 × 100 Hz) of LC	LTD ↓↓	>4 h	Lemon and Manahan-Vaughan (2011)
<b>(C) Effects of DA on hippocampal depotentiation by D1/D5 receptors</b>						
In vitro electrophysiology						
D1/D5 agonist	Before LFS	CA1	LFS (2 Hz, 10 min)	Depotentiation↓	40 min	Otmakhova and Lisman (1998)
In vivo electrophysiology						
D1/D5 agonist	Before LFS	CA1	LFS (600 × 5 Hz)	Depotentiation↓	25 h	Kulla and Manahan-Vaughan (2000)
D1/D5 agonist	Before LFS	DG	LFS (600 × 5 Hz)	Depotentiation↓	25 h	Kulla and Manahan-Vaughan (2000)
D1/D5 antagonist	Before LFS	CA1	LFS (600 × 5 Hz)	Prevented inhibition of depotentiation	25 h	Kulla and Manahan-Vaughan (2000)
D1/D5 antagonist	Before LFS	DG	LFS (600 × 5 Hz)	Prevented inhibition of depotentiation	25 h	Kulla and Manahan-Vaughan (2000)

D: dopamine; DG: dentate gyrus; E-LTD/LTP: early long-term depression/potentiation; HFS: high-frequency stimulation; LC: locus coeruleus; LFS: low-frequency stimulation; L-LTD/LTP: late long-term depression/potentiation; LTD: long-term depression; LTP: long-term potentiation; p: pulses; PP: perforant path; SC: Schaffer collaterals; SUB: subiculum; S1 or 2: synaptic input 1 or 2.

(Kemp and Manahan-Vaughan 2007). For this phenomenon, like LTP, D1/D5 receptors also appear to play a pivotal role. In contrast to LTP, where the CA1 region and the DG have been intensively studied, so far, information only exists with regard to D1/D5 receptor effects on LTD in the CA1 region (Table 1B).

E-LTD, induced by LFS of CA1 synapses, is facilitated by D1/D5 receptor agonism in vitro (Chen et al. 1995; Liu et al. 2009). By contrast, E-LTD is blocked by a D1/D5 receptor

antagonist in CA1 synapses in vitro (Chen et al. 1995). Furthermore, in vitro studies showed that both E- and L-LTD in CA1 synapses are dependent on D1/D5 receptor activation (Mockett et al. 2007; Liu et al. 2009). In vivo data agree with these results, as D1/D5 receptor agonism facilitates LFS-induced E-LTD and L-LTD, whereas D1/D5 receptor antagonism prevents LFS-induced E-LTD and L-LTD (Lemon and Manahan-Vaughan 2006). However, in one in vitro study, D1/D5 receptor agonism partially reversed LFS-induced LTD

(Mockett et al. 2007). These different in vitro effects could be due to the use of different LFS protocols [ $1200 \times 3$  Hz (Mockett et al. 2007) vs.  $450 \times 1$  Hz (Chen et al. 1995)] that evoke LTD of differing magnitudes and durations. In vivo, 1-Hz LFS using  $<600$  pulses elicits very short-term depression (STD) at CA1 synapses (Popkirov and Manahan-Vaughan 2011), whereas 3-Hz stimulation elicits more prolonged effects (Manahan-Vaughan 2000). Differences in the regulation of D1/D5 receptor agonists of synaptic depression of different strengths and durations may functionally relate to the relevance of these forms of plasticity for information processing: Weak responses may be strengthened and strong responses could conceivably become weakened, so that information processing is optimized.

### D1/D5 Receptors and Learning-Facilitated Plasticity

In vivo studies showed that learning-facilitated E-LTP and L-LTP by exploration of novel empty space can be prevented by D1/D5 receptor antagonism in CA1 synapses (Li et al. 2003; Lemon and Manahan-Vaughan 2006). Furthermore, the pharmacological activation of D1/D5 receptors mimics the spatial novelty-induced facilitation of LTP (Li et al. 2003). D1/D5 receptor agonism facilitates STD into LTD in CA1 synapses in vivo (Lemon and Manahan-Vaughan 2006). This supports the possibility that D1/D5 receptor activation lowers the threshold for CA1 LTD. In addition, a role for D1/D5 receptors in learning-facilitated LTD has been reported. Here, L-LTD that was facilitated by novel spatial exploration was prevented by D1/D5 receptor antagonism (Lemon and Manahan-Vaughan 2006). Novel spatial exploration concomitant with afferent stimulation combined with D1/D5 receptor activation also enables a slow-onset depression in CA1 synapses, thereby also supporting that D1/D5 receptor activation might lower the threshold for information storage by LTD in hippocampal synapses (Lemon and Manahan-Vaughan 2011; Table 1B). Thus, learning-facilitated E- and L-LTP can be modulated by activating D1/D5 receptors (Table 1A). Again, this finding links the D1/D5 receptors strongly to novel experience and suggests that these receptors may be one of the factors that confer salience and relevance to incoming sensory information reaching the hippocampus.

### What Enables the Differences in D1/D5 Regulation of Hippocampal Synaptic Plasticity?

Taken together, these studies support that D1/D5 receptors do not have identical effects on LTP in the CA1 region and DG. The CA1 region appears to be more sensitive, with both E-LTP and L-LTP being regulated by D1/D5 receptors. In the DG, by contrast, only L-LTP is affected. Adding to this functional spectrum is the regulation by D1/D5 receptors of LTD, depotentiation and learning-facilitated plasticity. This targeted regulation by D1/D5 receptors of so many different facets of synaptic plasticity may relate to the relative expression of D1/D5 receptors in the hippocampus, and the relative coupling of these receptors to signaling cascades. Both D1 and D5 receptors are both prominent in pyramidal cells of the hippocampus in monkeys (Bergson et al. 1995) and pyramidal neurons in the CA1–3, including cells in the stratum oriens and radiatum express D1/D5 receptors in rats (Fremeau et al. 1991). D1/D5 receptor mRNA is also localized dorsally in

granule cells of the DG and ventrally in most neurons of the subiculum complex (Fremeau et al. 1991). Furthermore, D5 receptors are expressed in the hilus and granule cells of the DG, in pyramidal cells of the subiculum, and in the CA1–CA3 region of rats, humans, and monkeys (Ciliax et al. 2000; Khan et al. 2000). Thus, a relatively even distribution of D1/D5 receptors occurs in the hippocampus. However, some differences in the neuronal localization of the D1 and D5 receptors appear to exist: D1 receptors in the cerebral cortex are found mainly on dendritic spines, whereas D5 receptors occur predominantly on dendritic shafts in the PFC (Bergson et al. 1995). These subcellular differences in the localization of D1/D5 receptors may have functional implications (Bergson et al. 1995). As the pyramidal dendritic spines receive excitatory glutamatergic (Harris and Kater 1994) and the dendritic shafts inhibitory gamma-aminobutyric acid (GABA)ergic input (Jones 1993), it is possible that D1 receptors are mainly involved in excitatory, and the D5 receptors in inhibitory, neuromodulation (Bergson et al. 1995).

Immunohistochemical investigations localized the D1 receptor to glutamatergic excitatory projection neurons of the granule cell layer of the DG and to multiple types of inhibitory GABAergic interneurons of the hilus and CA3/CA1 fields in the mouse hippocampus (Gangarossa et al. 2012). These GABAergic interneurons may regulate the synchronized output of the granule cells (Miles et al. 1996), indicating that DA acting on these interneurons may influence information processing in the hippocampal circuit. In the CA1 region of the hippocampus and PFC in the monkey, D1/D5 receptors are pre- and postsynaptically localized (Bergson et al. 1995), indicating pre- and postsynaptic DA-mediated mechanisms induce the modulation of synaptic strength. A tight regulation of excitability through the GABAergic system is an important factor not only in preventing LTP phenomena from escalating into epileptiform events, but also for LTD and the maintenance of synaptic excitability within a functional range (Baudry 1986; Wagner and Alger 1995; Kullmann et al. 2000).

Paradoxically, Gangarossa et al. (2012) showed that there are no D1 receptors in CA1 stratum radiatum of the mouse, although in this subregion D1/D5 receptor activation is necessary for hippocampal-dependent learning, memory (O'Carroll et al. 2006; Bethus et al. 2010), and persistent plasticity at SC–CA1 synapses (Lemon and Manahan-Vaughan 2006). This suggests that D5 receptors may be the prime mediators of effects on plasticity at SC–CA1 synapses. D1 receptors were found on TA–CA1 synapses, however (Gangarossa et al. 2012), suggesting that in contrast to SC–CA1 synapses, plasticity at TA–CA1 synapses may be regulated by D1 receptors.

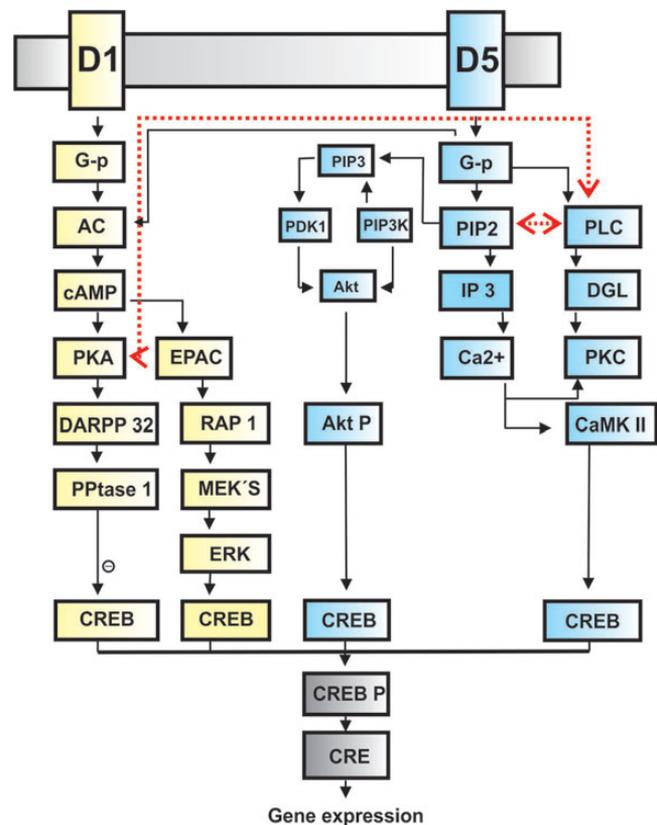
It is also important to point out that a mismatch between dopaminergic D1/D5 receptor distribution and dopaminergic fiber innervations of the hippocampus exists. Studies in rats demonstrated that the dorsal hippocampus receives dense noradrenergic innervations, but seldom dopaminergic innervation from the VTA (Swanson and Hartman 1975; Scatton et al. 1980). Furthermore, a discrepancy was observed between the robust immunostaining of D1/D5 receptors in the hippocampus and nearly-absent dopaminergic fibers (Smith and Greene 2012). dopaminergic fibers project from the VTA to the hippocampus (Scatton et al. 1980; Gasbarri et al. 1994, 1997), but this dopaminergic input from the VTA primarily targets the ventral hippocampus, and does not

innervate structures such as the stratum radiatum of the dorsal hippocampus (Swanson 1982; Gasbarri et al. 1994, 1997). This provokes the question as to how DA can influence dorsal hippocampal function at all. However, DA levels in the hippocampus do not just depend on dopaminergic innervations, as lesions in, for example, hippocampal noradrenergic neurons significantly reduce DA levels (Bischoff et al. 1979). Moreover, locus coeruleus (LC) fibers densely innervate the hippocampal formation including the stratum radiatum (Moudy et al. 1993) and enable a direct release of DA from noradrenergic LC fibers in the CA1 region (Smith and Greene 2012). It is thus possible that DA might be released from noradrenergic fiber terminals to “compensate” for the limited, or absent, VTA-mediated release of DA to the stratum radiatum and other dorsal hippocampal subregions, thus enabling DA to regulate synaptic plasticity and learning processes that are mediated by dorsal hippocampal structures.

D1/D5 receptors differentially regulate E-LTP and -LTP depending on the hippocampal subregions concerned (Huang and Kandel 1995; Otmakhova and Lisman 1996; Kulla and Manahan-Vaughan 2000; Lemon and Manahan-Vaughan 2006; Granado et al. 2008). A relatively different expression of D1 and D5 receptors could mediate this effect, in part, by influencing the different phases of LTP, due to the fact that the receptors engage different signal cascades. D1 receptor signaling is enabled via positive coupling to adenylyl cyclase (AC), whereas D5 receptor responses are predominantly mediated through positive coupling to phosphoinositide (Undieh 2010; Fig. 1). Thus, activation of either receptor will inevitably lead to phosphorylation processes, albeit of possibly different proteins. Both signal cascades (D1 and D5 receptors) converge ultimately on a common pathway converging on cAMP response element-binding protein (CREB) that supports long-term synaptic plasticity in the hippocampus (Barco et al. 2002).

Activation of AC via D1 receptors catalyzes the conversion of adenosine triphosphate to the intracellular second messenger cAMP. As a result, protein kinase A (PKA) activity, a target of cAMP, increases (Vallone et al. 2000; Undieh 2010). A target of PKA phosphorylation is the DA and cAMP-regulated 32-kDa phosphoprotein (DARPP-32) expressed in the DG of the hippocampus (DARPP-32; Undieh 2010), activation of which leads to potentiation of NMDA receptor function (Cepeda and Levine 2006). DA-sensitive PKA activation also regulates T-type  $Ca^{2+}$  currents (Drolet et al. 1997) and activation of the nuclear transcription factor calcium-response element-binding and CREB proteins leading to CREB protein expression (Undieh 2010; Fig. 1).

In contrast to D1 receptors, signaling via the phosphoinositide pathway of the D5 receptors activates phospholipase C (PLC), which induces hydrolysis of the phosphatidylinositol-4,5-bisphosphonate to produce the second messengers diacylglycerol and inositol-1,4,5-trisphosphate (Berridge and Irvine 1984). However, the activation of D5 receptors can also stimulate cAMP and the PKA pathway (Beaulieu and Gainetdinov 2011; Fig. 1). The formation of inositol phosphates causes a mobilization of intracellular calcium stores (Undieh 2010), that in turn, is critical step in the enablement of synaptic plasticity. Increased intracellular calcium activates calcium-calmodulin-dependent protein kinase type II leading to CREB activation (Fig. 1). Thus, activation of D1 and D5 receptors can lead to CREB activation via 2 distinct signaling pathways (Undieh 2010). Several crosstalks between the AC and PLC



**Figure 1.** Signal cascades of D1 and D5 receptors. Schematic demonstration of the different molecular pathways of D1 (yellow boxes) and D5 receptors (blue boxes) ending in a common CREB activation (gray boxes). Crosstalk between the D1/D5 system is indicated by red dashed lines. An inhibitory effect is signified by a circle containing a minus symbol. Abbreviations: AC: adenylyl cyclase; AktP: Akt phosphorylated; CaMKII: calcium-calmodulin-dependent protein kinase type II; cAMP: cyclic 3'5' adenosine monophosphate; CRE: cAMP response element; CREB: cAMP response element-binding protein; CREB P: CREB phosphorylated; DARPP-32: phosphoprotein of 32 kDa; DGL: diacylglycerol; D1: dopamine receptor 1; D5: dopamine receptor 5; EPAC: exchange protein activated by cAMP; ERK: extracellular signal-regulated kinase; G-p: G protein; IP3: inositol trisphosphate (IP3); by cAMP; ERK: extracellular signal-regulated kinase; MEK's: mitogen-activated kinases; PDK1: phosphoinositide-dependent kinase-1; PIP 2: phosphatidylinositol-4;5-bisphosphate; PIP3: phosphatidylinositol-3;4;5-triphosphate; PI3K: phosphatidylinositol-3-kinase; PKA: protein kinase A; PKC: protein kinase C; PLC: phospholipase C; PPtase 1: protein phosphatase 1; RAP 1: member of the RAS family of small GTP-binding proteins (Undieh 2010; Beaulieu and Gainetdinov 2011).

systems exist (Undieh 2010, Fig. 1). The coupling of different signal cascades of D1/D5 receptor activation may thus not only support different functions with regard to the regulation of phases of LTP, but also of LTD (Centonze et al. 2003) along with interactions with other receptors or neuromodulators (Liu et al. 2000) that in turn can influence the longevity of these plasticity phenomena.

As D1/D5 Receptors Stimulate Local Protein Synthesis in the Dendrites of Hippocampal Neurons (Smith et al. 2005), it is likely that D1/D5 receptors are involved in the protein translation that is required for L-LTP. In line with this, the blockade of hippocampal D1/D5 receptors (within 15 min of novelty exploration) blocks L-LTP and prevents place memory (Wang et al. 2010). Novelty exploration induces DA release, triggering an up-regulation of the immediate early gene *Arc* in the CA1 region (Guzowski et al. 1999). D1 receptor activation may also cause increases in *Zif268* and *Arc/Arg3.1* expression in the DG and both genes are involved in transcriptional

regulation and synaptic plasticity (Gangarossa et al. 2011). This suggests that DA, via D1/D5 receptors, stimulates transcriptional processes leading to long-term plasticity. Hippocampal D1/D5 receptors are specifically required to induce the synthesis of plasticity-related proteins necessary to consolidate long-term plasticity and memory (Moncada et al. 2011). The setting of a “synaptic tag” at a particular synapse for subsequent PRPs such as protein kinase M zeta (Navakkode et al. 2010) is essential for sustained LTP (Frey and Morris 1997). In vitro experiments suggest that D1/D5 receptor activation may be involved in this process (Sajikumar and Frey 2004; see Table 1). L-LTP inhibition by D1/D5 receptor antagonism can thus be explained on a molecular level by inhibited protein synthesis induced by the antagonism of these receptors.

The dual action of DA in inducing either LTD or LTP may be due to a concentration-dependent effect on different phosphorylation processes leading either in LTD or in LTP (Sajikumar and Frey 2004). The modulation of an NMDA receptor dependent form of both E-LTP and E-LTD via D1/D5 receptor activation in the CA1 region may be due to the fact that the DA signal converges on the NMDA receptor to induce ERK2 activation in this hippocampal subregion (Kaphzan et al. 2006). D1/D5 receptors also regulate the NMDA receptor directly (Cepeda et al. 1998; Stramiello and Wagner 2008; Varela et al. 2009) and could affect both LTP and LTD induction thresholds (Cummings et al. 1996), and signaling cascades activated by the D1/D5 receptors that lead to the activation of CREB and protein synthesis (Smith et al. 2005; Moncada et al. 2011; Sarantis et al. 2012). LTD is protein synthesis dependent (Manahan-Vaughan et al. 2000). Due to the fact that antagonism of D1/D5 receptors prevents LTD maintenance (Sajikumar and Frey 2004) in a manner similar to protein synthesis inhibitors (Sajikumar and Frey 2003), it is tempting to postulate that DA might be directly be involved in

processes required for the synthesis of plasticity-related proteins that not only relate to LTP, but also to LTD (Sajikumar and Frey 2004).

### Effect of D1/D5 Receptor Activity on Hippocampus-Dependent Learning

The aforementioned findings suggest that a very tight link exists between the regulation of synaptic plasticity by D1/D5 receptors and their role in hippocampus-dependent learning. The hippocampus plays a crucial role in learning and memory (Eichenbaum et al. 1990; Mishkin et al. 1998) and is involved in spatial and episodic memory (Burgess et al. 2002). The dopaminergic midbrain participates in human episodic memory formation (Schott et al. 2006). Furthermore, in rodents, long-term memory of hippocampus-mediated acquisition of new paired associates (episodic-like memory task) requires the activation of D1/D5 receptors. In contrast, early memory is unaffected by D1/D5 receptor antagonism (Bethus et al. 2010), and DA has no effect on already-established memories or on retrieval (O'Carroll et al. 2006; Table 2).

D1 agonist treatment in rats enhances hippocampus-dependent spatial memory (Bach et al. 1999; da Silva et al. 2012) without affecting nonspatial memory (da Silva et al. 2012). By contrast, D1/D5 receptor antagonists impair short- and long-term spatial memory (Clausen et al. 2011; da Silva et al. 2012). Studies in transgenic mice suggest that the D1 receptor (El-Gundi et al. 1999) and not the D3 or D5 receptor are essential for spatial learning (Granado et al. 2008; Xing et al. 2010). The D1 receptor is also crucial for the encoding of novel environments and hippocampal representations of plasticity (Tran et al. 2008). The D1 receptor is critical for the induction of Zif268 and arc, proteins required for the transition of E-LTP into L-LTP and memory consolidation in

**Table 2**  
D1/D5 receptors and hippocampus-dependent learning

Drug/knock out	Application route	Learning apparatus and/or learning task	Effect on learning	Reference
D1/D5 agonist	Intraperitoneal infusion	Barnes maze	Spatial memory↑	Bach et al. (1999)
D1/D5 agonist	Intra CA1 infusion	Water maze	Spatial memory↑	daSilva et al. (2012)
D1/D5 agonist	Intrahippocampal infusion	Inhibitory avoidance task	No effect on nonspatial Fear long-term memory↑ L-LTP↑	Rossato et al. (2009)
D1/D5 antagonist	Intrahippocampal infusion	Special event arena	Spatial memory↑	Bethus et al. (2010)
D1/D5 antagonist	Intra CA1 infusion	Water maze	Spatial memory formation↓	da Silva et al. (2012)
D1/D5 antagonist	Systemic/prelimbic infusion	Cross maze, open field	Spatial short-term memory↓	Clausen et al. (2011)
D1/D5 antagonist	Intrahippocampal infusion	Inhibitory avoidance task	Retrograde amnesia	Bernabeu et al. (1997)
D1/D5 antagonist	Intrahippocampal infusion	Fear long-term memory↓		Rossato et al. (2009)
D1/D5 antagonist	Intraventricular subiculum infusion	Instrumental learning task	Instrumental learning↓	Andrejewski et al. (2006)
D1/D5 antagonist	Intradorsal subiculum infusion	Instrumental learning task	No effect on instrumental learning	Andrejewski et al. (2006)
D1/D5 antagonist	Intrahippocampal infusion	Open-field water maze	Long-term memory↓	O'Carroll et al. (2006)
D1/D5 antagonist	Systemic/prelimbic infusion	Open field	Short-term object retention↓	Clausen et al. (2011)
D1 knock out	–	Morris water maze	Spatial learning↑	Xing et al. (2010)
D1 knock out	–	Morris water maze	Spatial learning↓	El Ghundi et al.(1999)
D1 knock out	–	Open field (square/circular)	Spatial learning↓ Spatial learning↓	Tran et al. (2008)
D1 knock out	–	Morris water maze	Spatial learning↓ E- and L-LTP↓	Granado et al. (2008)
D1 knock out	–	Barnes maze Elevated plus maze Passive avoidance task	Spatial and fear learning↓	Ortiz et al. (2010)
6-Hydroxydopamine-lesion	–	Fear conditioning/extinction Morris water maze	Spatial navigation↓ Memory for place navigation↓	Gasbarri et al. (1996)

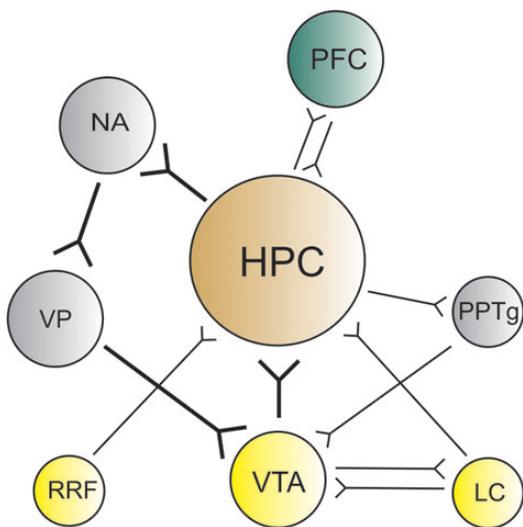
E-LTP and L-LTP: early and late long-term potentiation, respectively.

mammals (Granado et al. 2008), and the activation of D1/D5 receptors is required during memory encoding to generate a persistent memory trace in the hippocampus (O'Carroll et al. 2006). Learning-dependent changes in synaptic strength of other forms of hippocampal-dependent learning, such as classic eyeblink conditioning (Kuo et al. 2006, Suzuki 2007; Madronal et al. 2009), are also modulated by D1 receptor activation (Ortiz et al. 2010). These findings suggest that D1/D5 receptor activation is a crucial factor in the formation of spatial long-term memory in the mammalian brain.

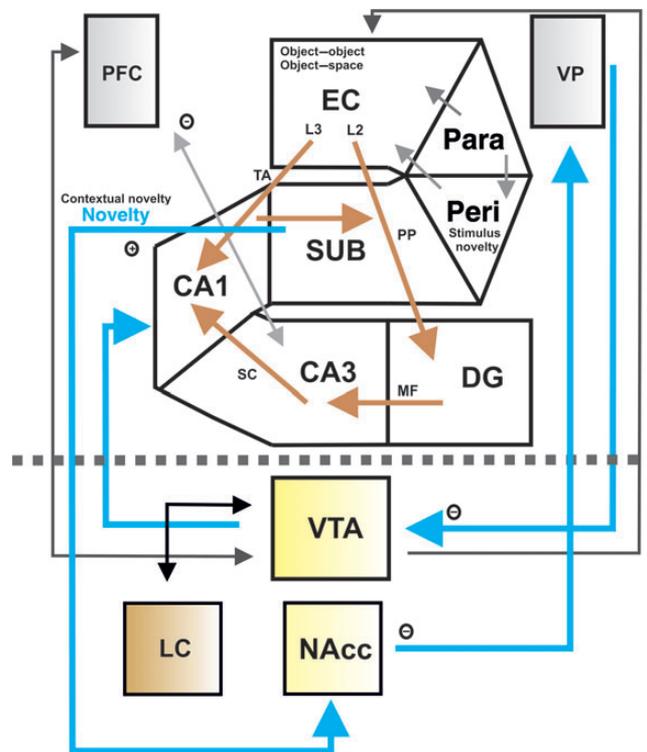
### The Role of the Novelty Signal

These observations raise the question as to what drives changes in DA levels in the hippocampus and the relative contribution of D1/D5 receptors to synaptic plasticity and memory formation. One major factor is the response to novelty. A highly significant source of DA release in the hippocampus derives from the VTA, the dopaminergic neurons of which discharge in response to novel stimuli (Ljunberg et al. 1992; Grenhoff et al. 1993) with a phasic burst pattern (Ljunberg et al. 1992). As the latencies of the response to a novel stimulus are quite similar between the VTA and hippocampus (50–200 ms), Lisman and Grace proposed a theoretical model illustrating how novel information is first processed by the hippocampus and secondly, leads to indirect activation of the VTA via the NAcc and VP. The indirect activation of the VTA occurs through an excitatory glutamatergic projection from the subiculum to the NAcc, an inhibitory GABAergic projection of the NAcc to the VP, and finally, an inhibitory GABAergic projection of the VP to the VTA (Legault et al. 2000; Floresco et al. 2001, Legault and Wise 2001; Figs 2 and 3).

It has been suggested that stored sensory information in the DG–CA3 system sends “predictive” information to the CA1 via the SC that “compares” the actual novel sensory data from



**Figure 2.** Anatomical connections between the hippocampus and dopaminergic nuclei. The VTA, retrorubral field (RRF), and LC all send projections to the hippocampus (HPC). The hippocampus in turn projects, on the one hand, to the NAcc that is connected with the VTA (hippocampal–VTA loop) and substantia nigra (SN) by the VP. On the other hand, the hippocampus projects to the pedunculopontine tegmentum (PPTg) that sends projections to the VTA and SN. Additionally, the PFC sends and receives projections from the hippocampus.



**Figure 3.** Regulation of hippocampal synaptic plasticity by the VTA and other dopaminergic nuclei. The dopaminergic regulation of hippocampal synaptic plasticity and the underlying network is depicted here. Blue arrows indicate the novelty activated VTA–hippocampal loop. The novelty signal is mediated from the perirhinal cortex (PERI) to the entorhinal cortex (EC). Additionally, the EC conveys object and space information to the DG and CA1. Here, the information is integrated to “object-in-context” representations and then processed via the NAcc and VP as the descending arc of the hippocampal–VTA loop to the VTA. The gray and black arrows show the different projections between the dopaminergic brainstem nuclei and the brain structures referring to the hippocampus and VTA involved in the dopaminergic modulation of hippocampal synaptic transmission. The gray dashed line indicates the separation of the cerebellum and brainstem. An inhibitory projection is indicated by a circle containing a minus symbol and an excitatory projection is indicated by a circle combined with a plus symbol. In this figure not all, but rather the main connections are shown. Abbreviations: EC: entorhinal cortex, LC: locus coeruleus, L2/3: layer 2/3 of the EC, MF: mossy fibers, NAcc: nucleus accumbens, PARA: parahippocampus, PERI: perirhinal cortex, PP: perforant path, SC: Schaffer collaterals, SUB: subiculum, TA: temporoammonic pathway, VP: ventral palladium, VTA: ventral tegmental area. (Simon et al. 1979; Grace 1991; Howland et al. 2002; Lisman and Grace 2005; Yin et al. 2008; Sara 2009; Lisman et al. 2011).

the perforant path. This resulting “mismatch” signal activates the VTA via the indirect pathway (NAcc and VP) of the hippocampal–VTA loop (Lisman and Grace 2005). Neuroimaging studies in humans support the hippocampal–VTA-dependent encoding of novel stimuli (Wittmann et al. 2005; Adcock et al. 2006). Further neuroimaging data in humans highlighted the coactivation of the VTA, hippocampus, and VP by stimulus novelty (Bunzeck and Düzel 2006), and an in vivo study in rats showed that novel stimuli induced a rise in DA in the NAcc dependent on information processing from the ventral subiculum of the hippocampus (Legault and Wise 2001).

Taken together, these findings support that novel information may first be registered by the hippocampus that in turn activates the VTA to generate the novelty signal that subsequently influences qualitative hippocampal information encoding. In line with this, an enhancement of long-term plasticity in the DG induced by HFS is observed when a rat is placed in a novel environment (Davis et al. 2004), suggesting

that novelty has a marked influence on hippocampal excitability. Accordingly, novelty induces a rise in hippocampal activity in rabbits (Vinogradova 2001), rats (Jenkins et al. 2004), and humans (Tulving et al. 1996; Strange and Dolan 2001). Furthermore, it is the hippocampus and not the VTA that appears to initiate the novelty response: Event-related potentials in the hippocampus of the cat (Ruusurvita et al. 1995) and rat (Brankack et al. 1996) indicate that the hippocampus triggers novelty-related firing of the VTA. Correspondingly, DA release occurs after novel stimuli in the mouse hippocampus (Ihalainen et al. 1999) and hippocampal novelty signals increase the number of tonically activated DA VTA neurons (Floresco et al. 2003; Figs 2 and 3). The dialog between hippocampus and VTA appears essential for long-term information storage. Thus, a reciprocal interaction of the VTA/hippocampus circuit enables the encoding of novel information into long-term memory by VTA DA release (Mizumori et al. 2004; Lisman and Grace 2005; Wittmann et al. 2005; Adcock et al. 2006).

Processing of novelty by the hippocampus, however, may be supported by structures other than the VTA. For example, the noradrenergic LC fires rhythmically in response to novel experience (Sara et al. 1994). Activation of this structure changes hippocampal excitability (Kitchigina et al. 1997) and facilitates synaptic plasticity (Lemon et al. 2009). But the LC and the VTA are interlinked on both functional and anatomical levels. A study using anterograde and retrograde tracing techniques showed that the LC and VTA have anatomical connections (Simon et al. 1979). The VTA projects directly to the LC and is likely to release DA there, indicating a feedforward connection between the VTA and LC (Ornstein et al. 1987; Sara 2009). Moreover, the VTA can induce PFC activation via DA release that, in turn, alters LC neuronal activity via glutamate release (Sara 2009), and VTA DA neurons are modulated via noradrenaline that is released as a consequence of electrical stimulation of the LC (Grenhoff et al. 1993). Lesions studies of LC noradrenaline neurons and VTA DA neurons suggest that LC noradrenaline neurons and VTA DA neurons exert an inhibitory influence on DA neurons firing in the VTA and noradrenaline neurons in the LC, respectively (Guiard et al. 2008). However,  $\alpha$ 1-receptor antagonism by prazosin in LC revealed a decrease in DA neuron firing in the VTA, suggesting an excitatory effect of LC noradrenaline neurons to the VTA DA neurons as well (Grenhoff and Svensson 1993). Thus, the LC engages in a complex functional dialog with the VTA.

Both the LC (Vankov et al. 1995) and VTA (Schultz et al. 1993) neurons are activated by novelty, acting as learning signals in a complementary fashion (Harley 2004). Whereas the LC becomes immediate active when novel experience commences (Aston-Jones and Bloom 1981; Sara et al. 1994), the VTA becomes active within hundreds of milliseconds later (Ljungberg et al. 1992). This suggest that the LC, either via direct communication with the VTA, or via the hippocampus-VTA loop, may regulate DA release from the VTA to the hippocampus. In line with this possibility, D1/D5 receptors are involved in regulating hippocampal LTD that is induced by LC stimulation (Lemon et al. 2009; Lemon and Manahan-Vaughan 2011). Here, D1/D5 receptor antagonism prevents LC-CA1 LTD. Furthermore, application of a D1/D5 receptor agonist facilitates LC-induced CA1 E-LTD into L-LTD that lasts for over 24 h (Lemon and Manahan-Vaughan 2011; Table 1B). These findings suggest that the D1/D5 receptor system serves to

lower the threshold required for persistent storage of information under conditions of novelty or increased arousal regardless of the source of the novelty signal (Lemon and Manahan-Vaughan 2011).

### D1/D5 Receptors are Pivotal for Hippocampal Information Storage

Based on current knowledge, it is clear that D1/D5 receptors play an intriguing and decisive role in the enablement of information encoding and storage in the hippocampus. They can facilitate the expression of both LTP and LTD, and taking into account the accumulating evidence that LTP encodes different aspects of spatial representations (Kemp and Manahan-Vaughan 2007, 2008a; Goh and Manahan-Vaughan 2012), this suggests that D1/D5 receptors can drive the nature and qualitative content of stored information in the hippocampus. Strikingly, on a functional level and in line with this postulate, D1/D5 receptor activation leads to increased processing within the trisynaptic DG-CA3-CA1 circuit, to the disadvantage of the direct entorhinal-CA1 input (Varela et al. 2009), thereby minimizing the influence of mismatch detection (Lisman and Otmakhova 2001) in favor of prioritizing information storage. This in turn is likely to be highly relevant in the coupling of information storage and memory with reward experiences.

Taken together with the observations that D1/D5 receptor activation modulates hippocampus-dependent episodic and spatial long-term memory, these data indicate that D1/D5 receptors gate hippocampal long-term plasticity and memory in the mammalian brain, and are pivotal in conferring the properties of novelty and reward to information being processed by the hippocampus.

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### Notes

*Conflict of Interest:* None declared.

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