Neuron, Vol. 46, 703–713, June 2, 2005, Copyright ©2005 by Elsevier Inc. DOI 10.1016/j.neuron.2005.05.002

The Hippocampal-VTA Loop: Controlling the Entry of Information into Long-Term Memory

Review

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In this article we develop the concept that the hippocampus and the midbrain dopaminergic neurons of the ventral tegmental area (VTA) form a functional loop. Activation of the loop begins when the hippocampus detects newly arrived information that is not already stored in its long-term memory. The resulting novelty signal is conveyed through the subiculum, accumbens, and ventral pallidum to the VTA where it contributes (along with salience and goal information) to the novelty-dependent firing of these cells. In the upward arm of the loop, dopamine (DA) is released within the hippocampus; this produces an enhancement of LTP and learning. These findings support a model whereby the hippocampal-VTA loop regulates the entry of information into long-term memory.

The hippocampus is a temporal lobe structure that is vital for the encoding and recall of episodic memory (Squire et al., 2004). It has various functional states under the control of neuromodulators (Hirase et al., 2001). There has been considerable investigation of the modulation produced by noradrenaline and acetylcholine (Hasselmo, 1995; Murchison et al., 2004), but the role of dopamine (DA) has been less extensively studied because of the early view that the hippocampus did not receive a significant dopaminergic innervation (Loy et al., 1980). It is now clear that the hippocampus does receive such innervation (Gasbarri et al., 1997) and there has been progress in understanding its function. Specifically, work in the field of synaptic plasticity has provided clear evidence that DA affects long-term potentiation (LTP), a form of synaptic plasticity thought to encode long-term memory. In parallel, investigators in the field of CNS physiology have sought to determine the conditions under which DA cells fire. It has been shown that the burst firing of these cells is increased by unexpected rewards and reduced if an expected reward is omitted (Schultz and Dickinson, 2000). However, firing can also be triggered by novel stimuli that do not involve reward (Horvitz et al., 1997; Ljungberg et al., 1992; Steinfels et al., 1983). Recent work has shown that the pathways responsible for this novelty-dependent dopaminergic activity can be traced back to the hippocampus (Legault and Wise, 2001). Here we review the developments in these two fields and offer a new perspective: viewed in an integrated manner, these developments strongly suggest that the hippocampus and VTA form a functional loop designed to detect novelty and to use this novelty signal to control the entry of behaviorally significant information into the hippocampal store of long-term memory.

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The Role of the Hippocampus in Producing Novelty-Dependent Firing of VTA Cells

Recordings from dopaminergic cells in awake monkeys and cats have shown that these cells respond rapidly with bursts of spikes to novel stimuli (Ljungberg et al., 1992; Steinfels et al., 1983) and that as these stimuli become familiar, the DA neurons no longer show this change in activity (Figure 1B). In such experiments there is a motor component that signals the animal's response, but the firing is not related to this motor component; changes in firing do not occur during the response unless the stimuli are novel or rewarding (Kilpatrick et al., 2000; Schultz, 2000).

Because the computation of novelty requires the comparison of incoming information with stored memories, this computation might be expected to occur in the hippocampus. Several lines of information indicate that this is indeed the case. Single-unit recordings (Fyhn et al., 2002; Vinogradova, 2001) and imaging studies using PET (Tulving et al., 1996), fMRI (Strange and Dolan, 2001; Yamaguchi et al., 2004), and c-Fos expression (Jenkins et al., 2004) all indicate that presentation of a novel stimulus produces a robust increase in hippocampal activity. Importantly, measurements of hippocampal evoked responses (Grunwald et al., 1998; Ruusuvirta et al., 1995) generated in CA1 (Brankack et al., 1996) indicate that a form of novelty (expected versus unexpected conditioned stimuli) can be detected in less than 100 ms (Figure 1A). The rapidity of this detection suggests that the hippocampus could be part of the circuit that initiates the short-latency novelty-dependent firing of the VTA and is not simply responding to it.

The role of the hippocampus in novelty detection is further supported by the finding that interfering with hippocampal function inhibits the orienting of rabbits to novel stimulus configurations (Honey et al., 1998; Vinogradova, 2001) and the novelty-initiated galvanic skin response in humans (Knight, 1996; Knight and Nakada, 1998). Furthermore, stimulation of the hippocampal region increases exploratory behavior in a manner similar to that produced by novelty itself (Flicker and Geyer, 1982; Yang and Mogenson, 1987).

The locus of novelty detection in the hippocampus is not known with certainty (Lee et al., 2005); the novelty signals observed in CA1 (Figure 1A) could be computed at an earlier stage and transmitted to CA1. However, there are reasons for suspecting that the computation is indeed made in CA1. The regions that precede CA1 (dentate and CA3) appear to have other functions. Specifically, the phase-precession of hippocampal place

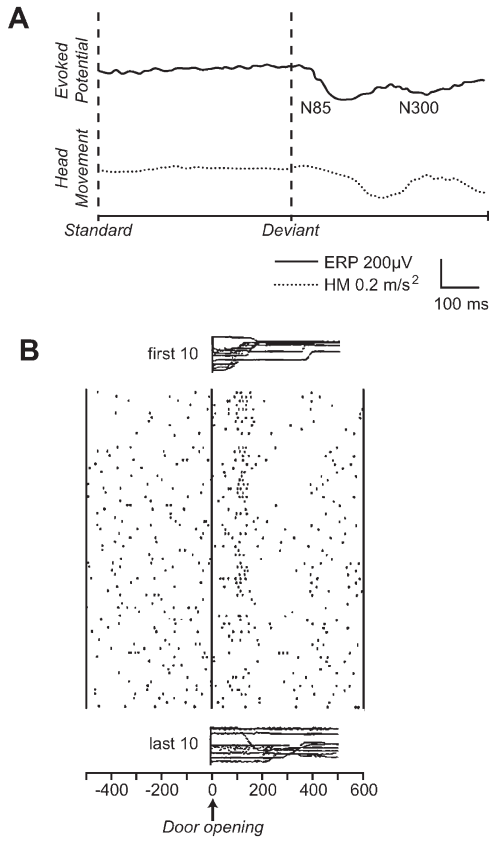

Figure 1. Rapid Responses to Novelty in the Hippocampus and VTA

(A) In the hippocampus after conditioning, there is a rapid field potential response (upper trace) to novel auditory stimuli, but not to the standard tones intermixed with the novel tones. The lower trace is the electromyographic responses indicating the orienting of the animal to the novel stimuli. Recordings in awake cats. (Adapted from Ruusuvirta et al., 1995, Figure 2; used with permission from Elsevier).

(B) Raster display showing spike firing from a VTA DA neuron. This neuron initially shows a rapid response to a novel stimulus (i.e., door opening, indicated by the arrow; each line is a single trial). With repeated presentation (top to bottom), the response habituates. Upper traces show eye movements, which are evoked by novel stimuli before habituation occurs. Lower traces show rare eye movements after habituation. (Adapted from Ljungberg et al., 1992, Figure 3A; used with permission from J. Neurophysiol.).

cells is observed in these regions and has been interpreted as the recall of a memory sequence cued by sensory input (Jensen and Lisman, 1996; Tsodyks et al., 1996). In such sequence recall, a sensory cue triggers a process within the dentate and CA3 that predicts the events (places) that are likely to happen next, based on stored memory sequences (Lisman, 1999). These predictions are then sent to CA1 via the Schaffer collaterals (Figure 5). CA1 cells also receive a second major input that comes directly from cortex and carries sensory information (Vinogradova, 1984). Thus, an attractive possibility suggested in many computational models (reviewed in Hasselmo and Wyble, 1997) is that novelty is computed in CA1 through a process that compares the predictions that arrive from CA3 with the "reality" that arrives directly from cortex. According to this view, CA1 acts as a "comparator" that computes novelty.

The Subiculum Is Necessary and Sufficient for the Dopamine Novelty Response

Whatever the exact site of novelty detection within the hippocampal region, there is now evidence for a polysynaptic pathway (Figure 5) that carries that novelty signal from the hippocampus to the VTA. Legault and Wise (2001) generated a behaviorally significant novelty event by allowing rats to enter a part of their cage from which they were previously restricted. This event led to substantial activation of the VTA, as evidenced by the DA released in a VTA target, the nucleus accumbens (Figure 2A1).

To test whether this release was dependent on the hippocampus, TTX was injected into the ventral subiculum, an output structure of the hippocampus that receives direct excitatory input from CA1. TTX caused a nearly complete block of the novelty-induced DA release (Figure 2A2). The release could also be reduced by blocking glutamate receptors in the VTA, ruling out the possibility that DA release was due solely to an effect on DA terminals in the accumbens, where the release was measured. These results thus demonstrate that the hippocampal region is necessary for generating the novelty-dependent activation of the VTA.

Related experiments have shown that stimulation of the subiculum is sufficient to cause DA release. Specifically, exciting the subiculum with tetanic stimulation (Blaha et al., 1997; Taepavarapruk et al., 2000), NMDA application (Floresco et al., 2001; Floresco et al., 2003) (Figures 2B and 2C), or by block of inhibition (Figure 2D) produces activation of the VTA. The most dramatic change involves the number of VTA cells firing rather than their rate of discharge (Floresco et al., 2001; Floresco et al., 2003).

The Polysynaptic Pathway from Hippocampus to VTA

One possible route of information flow from the hippocampus to the VTA is through the prefrontal cortex (PFC) because there are excitatory connections from the hippocampus to the PFC and from the PFC to the VTA. However, this route does *not* seem to be critical for hippocampal-dependent VTA activation because TTX application to the PFC does not block the effect of subicular stimulation on DA neuron activity (Floresco et al., 2001) (Figure 2C2). Rather, the evidence indicates that the signal involves a polysynaptic pathway through the accumbens and ventral pallidum (Figure 2C2). The activation of DA neurons caused by stimulation of the subiculum can be blocked by application of a glutamate receptor antagonist into the accumbens (Floresco et al., 2001). Since accumbens cells are a major target of excitatory input from the subiculum, these results suggest that the accumbens is required to relay information from the hippocampus to the VTA (Floresco et al., 2001; Legault et al., 2000). Accumbens neurons have been shown to fire in response to novelty (Ihalainen et al., 1999) or subicular stimulation (Wood and Rebec, 2004).

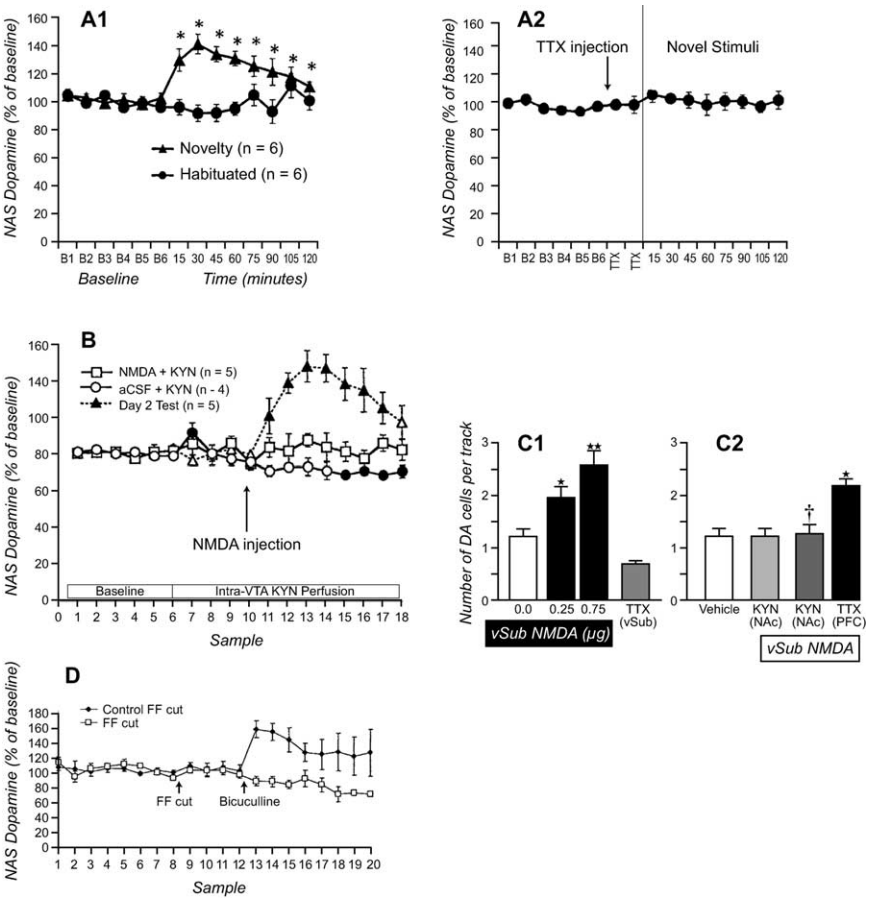

Figure 2. Pathway from the Hippocampus to the VTA

(A1) Putting a rat in a novel cage, but not a familiar cage evokes DA release in the accumbens. (A2) The novelty-dependent release of DA is blocked by TTX injection into the subiculum. (Adapted from Legault and Wise, 2001, Figures 1 and 2; used with permission from Blackwell Publishers, Ltd.). (B) DA can be released in the accumbens by exciting the subiculum with NMDA injection (filled triangles); this release is dependent on the VTA because injecting a glutamatergic antagonist (KYN) into the VTA blocks the DA release (open squares). (Adapted from Legault et al., 2000, Figure 3; used with permission from the Society for Neuroscience). (C1) NMDA application to the subiculum produces a dose-dependent increase in the number of spontaneously firing DA cells, but not if TTX is present in the subiculum. (C2) This increase is blocked by KYN injection into the accumbens, but not by TTX injection into the prefrontal cortex (PFC). (Adapted from Floresco et al., 2001, Figure 2; used with permission from the Society for Neuroscience). (D) Another method for exciting the subiculum is by injecting the GABA antagonist, bicuculline. This also evokes DA release from the accumbens, provided that the fibria/fornix is intact. (Adapted from Mitchell et al., 2000, Figure 5A; used with permission from Elsevier).

The next relay stage appears to be the ventral pallidum, which receives a strong GABAergic inhibitory input from the accumbens. The ventral pallidum consists primarily of rapidly firing GABAergic neurons, which are known to innervate the VTA dopaminergic neurons (Chrobak and Napier, 1993; Mogenson et al., 1993). It has been shown that inhibition of the ventral pallidum by direct infusion of GABA A/B agonists increases the number of DA neurons that are active (because of disinhibition), mimicking the effect of subicular stimulation (Floresco et al., 2003). Taken together, these results are consistent with the following pathway: the subiculum sends excitatory glutamatergic projections to the accumbens, which in turn inhibits the ventral pallidum, thus releasing the VTA DA neurons from a tonic inhibitory influence (Figure 5). The pathway we have described forms the downward arc of the hippocampal-VTA loop. In the next section, we consider the upward arm of this loop in which the VTA affects the hippocampus.

The Effect of DA on LTP

The hippocampus receives dopaminergic input (Scatton et al., 1980), which comes from both the substantia nigra and the VTA. The distribution of input is uneven, being particularly strong in the subiculum, hilus, and the stratum lacunosum-moleculare of the CA1 region (Gasbarri et al., 1994; Gasbarri et al., 1997; Goldsmith and Joyce, 1994). Both D2 (Brouwer et al., 1992; Mengod et al., 1992; Swanson et al., 1987; Yokoyama et al., 1994) and D1 receptor families (i.e., D1 and D5 receptor subtypes) are found in the hippocampus (Gingrich et al., 1992; Huang and Kandel, 1995). It now appears that the D5 receptor (which is also responsive to D1-type drugs) is the primary subtype of the D1 family of receptors found in the hippocampus (Laurier et al., 1994;

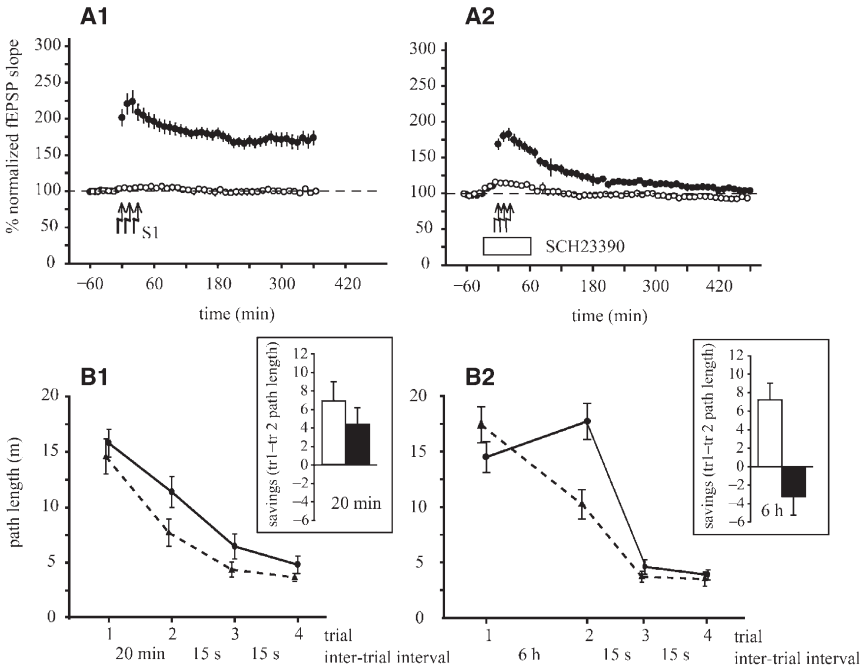

Figure 3. Interfering with Dopamine Action Blocks Late LTP and 6 hr Memory

(A1) LTP (closed circles) in the CA1 region of a slice preparation is induced by three tetani (100 Hz); no LTP occurred in the control pathway (open circles). (A2) The same stimulation given in the presence of the D1 antagonist SCH23390 produced only early LTP. (B1 and B2) Bilateral infusion of SCH23390 into the hippocampus blocked a form of learning. The path length refers to the average distance traveled to find a reward site, which becomes shorter with learning. On each day, the rat is allowed four trials to find a day-unique rewarded site (the intertrial interval is varied). On the second trial, learning in the presence of the D1 antagonist (solid lines) is worse than normal (dashed lines). The deficit is large if the intertrial interval is long (6 h), as in (B2); the deficit is small if the intertrial interval is only 20 min (B1). (Reprinted from Morris et al., 2003, Figure 4; used with permission from The Royal Society).

Meador-Woodruff et al., 1992; Sokoloff and Schwartz, 1995). Much of the enzymatic machinery that is associated with dopaminergic transmission is present in the hippocampus, including DA uptake sites (Mennicken et al., 1992), the DA metabolizing enzyme, COMT (Matsumoto et al., 2003), and DARPP-32 (Sakagami et al., 1994).

Experiments in hippocampal slices show that LTP in CA1 is strongly dependent on DA. When strong, repeated stimulation is used to evoke LTP, the late phase of LTP is completely blocked in the D1 knockout. Similar blockage is produced by D1 antagonists (Bach et al., 1999; Frey et al., 1993; Frey et al., 1991; Frey et al., 1990; Huang and Kandel, 1995). The antagonist, in this case, is acting on DA released from dopaminergic axons by the LTP-inducing stimuli (Frey et al., 1990). A recent replication of this finding (Morris et al., 2003) (Figure 3A) is noteworthy because of the use of a second input pathway that was not tetanized; the stability of responses in this pathway proves that the decay of LTP in the tetanized pathway is not simply a result of a decline in the health of the preparation. The ability of a DA antagonist to block late LTP has also been demonstrated in vivo (Swanson-Park et al., 1999).

Conversely, LTP can be enhanced by activation of dopamine receptors. Early LTP can be enhanced by D1 activation, but this effect is significant only if the endogeneous release is reduced by depletion of endogenous pools (Otmakhova and Lisman, 1996). If stimulation parameters are adjusted so that only early LTP is induced, application of a D1 agonist enhances late LTP (Swanson-Park et al., 1999). Even weaker stimulation that normally produces no potentiation will produce LTP (Figure 4B) after systemic application of a D1 agonist (Li et al., 2003).

It appears that a major component of dopamine action can be understood in terms of the known effects of D1 receptors in stimulating adenylate cyclase and producing a rise in cAMP. Stimulating the cyclase directly with forskolin similarly enhances LTP (Frey et al., 1993; Otmakhova and Lisman, 1996). A second action of dopamine on plasticity, i.e., inhibition of depotentiation, is also mimicked by forskolin (Otmakhova and Lisman, 1998). One important action of cAMP is to stimulate PKA. Activation of this kinase, in turn, acts to inhibit phosphatase activity and thereby enhances the phosphorylation of CaMKII (Blitzer et al., 1998), a molecule that is necessary and sufficient (in its phosphorylated, active state) for producing LTP (reviewed in Lisman et al., 2002). These reactions provide a basis for the dopaminergic modulation of early LTP. Progress has also been made in understanding the special importance of dopamine in late LTP. Interestingly, both late LTP (Figure 3A) and late LTD are dependent on dopamine and require protein synthesis (Sajikumar and Frey, 2004). The dopamine-induced elevation of cAMP pro-

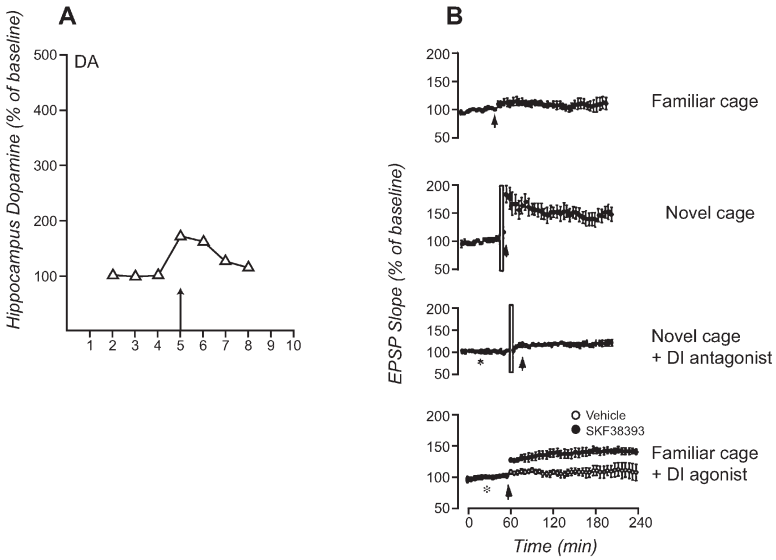

Figure 4. Novelty-Dependent DA Release in the Hippocampus Enhances In Vivo LTP in the Hippocampal CA1 Region

(A) Exposure of the rat to a novel environment evokes hippocampal DA release as measured by microdialysis and HPLC. (Adapted Ihalainen et al., 1999, Figure 1; used with permission from Elsevier).

(B) (top) A weak tetanus to the Schaffer collateral input to CA1 pyramidal cells fails to evoke LTP when the animal is placed in a familiar cage. (Second down). After the animal is placed is a novel cage, the same stimulus evokes LTP. (Third down) This LTP can be blocked by a systemic D1 antagonist. (Bottom) Conversely, systemic application of a D1 agonist allows the stimulus to evoke LTP even in the familiar cage. (Adapted from Li et al., 2003, Figures 1, 3, and 4; used with permission from Nature http://www.nature.com/).

duces a PKA-dependent activation of CREB (Pittenger et al., 2002). Furthermore, cAMP, acting via Rap1, leads to p42/44 MAPK activation (Morozov et al., 2003). Together these pathways stimulate the protein synthesis required for late LTP (Barco et al., 2002). Recent work using optical detection of protein synthesis allowed direct visualization of the rapid dopamine-induced stimulation of protein synthesis and showed that it occurred within the dendrites themselves (Smith et al., 2005).

Novelty-Dependent Enhancement of LTP

We have reviewed the evidence that a novel experience can activate DA neurons and that DA can enhance LTP. It follows that novelty itself should enhance LTP through dopamine release in the hippocampus, and there is now direct evidence that this is indeed the case. Measurements of DA in the hippocampus (Figure 4A) showed that putting a rat in a novel cage is sufficient to cause a robust increase in DA release (Ihalainen et al., 1999). It has further been demonstrated (Li et al., 2003) that exposure of rats to a novel environment enhances the ability of a weak tetanus to induce LTP in CA1 (Figure 4B). This enhancement is blocked by systemic injection of a D1 antagonist (Figure 4B), but not by noradrenergic and cholinergic blockers. Moreover, if the rat is left in a familiar cage, injecting a D1 agonist enhances LTP in a manner similar to that produced by placing the rat in a novel environment (Figure 4B). These results thus show that dopaminergic enhancement of LTP can be stimulated by natural novel stimuli. Dopamine appears to be an especially key modulator for LTP in CA1; cholinergic and noradrenergic antagonists did not block the novelty-induced enhancement of LTP (Li et al., 2003). This is in contrast to the dentate gyrus, where novelty-dependent changes are dependent on noradrenergic modulation (Kitchigina et al., 1997; Straube et al., 2003).

Effects of the Dopamine System on Memory in Rats

There is reasonable evidence from animal experiments that DA enhances learning, as would be expected from its enhancement of LTP. Packard and White (Packard and White, 1991) analyzed the effect of D1 and D2 agonists on the acquisition of an 8-arm radial maze and found that intrahippocampal injection of these agonists improved performance. Similarly, bilateral *injections* of a D1/D5 receptor agonist into the CA1 region of the dorsal hippocampus enhanced memory retention (Bernabeu et al., 1997). Bach et al. (Bach et al., 1999) found that systemic dopamine agonists strongly enhanced spatial memory in aged rats. Complementary findings have found that procedures that reduce DA action produce a decrease in memory (Bernabeu et al., 1997). Furthermore, DA *depletion within the hippocampus* impaired spatial navigation in the Morris water maze (Gasbarri et al., 1996). Importantly, a recent brief report shows that a D1 antagonist applied only to the hippocampus impairs memory (Figure 3B), especially when memory is tested at delays (6 hr) comparable to late LTP (Morris et al., 2003).

Effects of the Dopamine System on Human Memory

The study of the role of dopamine in human episodic memory is only in its infancy, but there are already fascinating findings. Enhancement of dopamine pools by administration of L-DOPA to normal subjects produces ~25% improvement in the memory of newly learned pseudowords (measured after 1 month) (Knecht et al., 2004). A second example involves the enzyme COMT, which metabolizes dopamine. Disruption of COMT increases dopamine levels without affecting the levels of other monoamines (Gogos et al., 1998). COMT has a gene polymorphism that affects the rate of dopamine metabolism. Carriers of the Met/Met genotype that is associated with lower COMT enzyme activity show better episodic memory than do carriers of the more active Val allele (de Frias et al., 2004). Consistent with this, preliminary results indicate that tolcapone, a COMT inhibitor, can enhance various forms of memory, including episodic memory (Iudicello et al., 2004). This confluence of evidence from animal and human research is

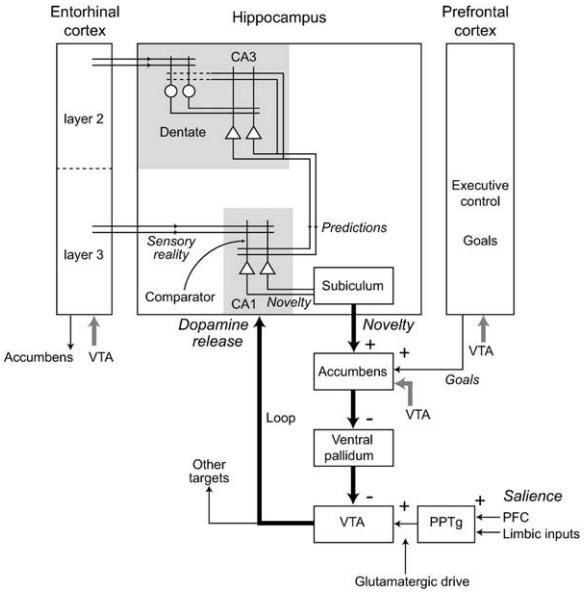

Figure 5. Connectivity within the Hippocampus and the Hippocampus-VTA Loop

Input to the dentate gyrus comes from layer 2 of the entorhinal cortex. The dentate/CA3 areas together store and recall sequences and provide input to CA1 which compares these predictions to direct cortical input from layer 3 of entorhinal cortex. Novelty signals from the CA1 comparator pass to the nearby subiculum, from there to basal forebrain structures, and from there to the midbrain dopamine cells of the VTA. The loop is completed by ascending dopamine fibers that innervate the hippocampus. See text for a description of the limbic inputs to the pedunculopontine tegmentum (PPTg).

further supported by recent fMRI data showing that VTA and substantia nigra midbrain regions in humans can be activated by reward or novelty (Schott et al., 2004; Uzakov et al., 2004; Wittmann et al., 2005), similar to the findings in rats and primates.

There is not yet any clear indication that deficits in human memory are related to decreases in dopamine availability. In Parkinson's disease, there is major degeneration of the substantia nigra. However, there is much less degeneration of the VTA, at least until late stages of the disease (Hirsch et al., 1988), which may account for why memory-related problems are not a major factor in the early stages of the disease.

Why Is the Downward Arc So Complex? Combining Novelty, Motivational Salience, and Reward to Control Attention and Learning

The pathway from the subiculum to the accumbens consists of thousands of cells and converges onto the medium spiny neurons of the accumbens (Figure 5) where other brain regions also make excitatory synapses. (French and Totterdell, 2002; French and Totterdell, 2003; O'Donnell and Grace, 1995). What is the reason for such complexity? Why isn't novelty converted into a scalar signal that could be conveyed by a small number of neurons directly to the VTA? We suggest that there are two reasons for this complexity. First, not all novel events may be of sufficient importance to enter into long-term memory. Indeed, there is so much novelty in the environment that were it all incorporated into memory, it could overwhelm memory capacity and overwrite preexisting information. This may be the reason that entry of information into long-term memory is regulated. In particular, the novelty signals (i.e., whether the object is new) from the hippocampus may interact with goal-related motivation and salience information (i.e., whether the object is behaviorally relevant) from other structures and thereby come to reflect the importance of the novel information. As described in the next paragraphs, there is beginning to be information about how the downward arc of the hippocampal-VTA loop performs this function.

The spiny cells in the accumbens are a likely site for combining novelty signals and goal-dependent motivational signals. Individual cells receive convergent inputs (French and Totterdell, 2002) from the hippocampus and from the prefrontal cortex (PFC), a source of goal-directed information. Biophysical analysis has provided insight into how these signals are combined. Spiny cells display a bistable subthreshold membrane property (O'Donnell and Grace, 1995). Although there has been some concern that such bistability may be a result of anesthesia, recent work shows that it is present in both awake animals (Petersen et al., 2003) and in a slice preparation without anesthesia (Tseng and O'Donnell, 2005). The up-state appears to be driven by NMDAR activation arising from hippocampal input (O'Donnell and Grace, 1998) and does not require dopaminergic modulation (West and Grace, 2002). PFC inputs can effectively fire spiny cells that are in the up state, but not those in the down state (O'Donnell and Grace, 1995; Kepecs and Raghavachari, 2002). This coincidence mechanism could thus serve to selectively relay to the VTA only novel information that is important within the goal set.

A second site at which multiple lines of information converge is the DA neurons themselves. As mentioned previously, these cells receive tonic inhibitory input from the ventral pallidum; removal of this inhibition occurs as a result of novelty-dependent activation of the descending pathways described above. In addition, DA neurons receive excitatory (glutamatergic) input and cholinergic input from the pedunculopontine nucleus, a region that is driven by a number of limbic afferents, including the prefrontal cortex, the bed nucleus of the stria terminalis, the hypothalamus, and the central nucleus of the amygdala; together, these provide both affect-related information (Semba and Fibiger, 1992) and information about the presence of salient stimuli (Kobayashi et al., 2002; Koyama et al., 1994). Activation of the pedunculopontine nucleus induces burst firing in DA neurons that depends on NMDA channel activation. However, such activation can only occur in cells that are firing spontaneously as a result of disinhibition of the subiculum-accumbens-ventral pallidum pathway (Floresco et al., 2003). Recent studies show that when the subiculum and pedunculopontine nucleus are activated together, there is a nearly 3-fold increase in the number of DA neurons firing in bursts (Lodge and Grace, 2005). Thus, it appears that the firing that occurs when stimuli are both novel and salient can be ex-

plained by the requirement for joint inputs to the DA cells of the VTA: an excitatory glutamatergic signal from the pedunculopontine nucleus representing stimulus saliency and a disinhibitory signal from the hippocampal-accumbens-pallidum pathway representing novelty. Although much remains to be learned about the downward arm of the hippocampal-VTA loop, we argue that the available evidence supports the reasonable working hypothesis that this arm combines novelty signals with information about salience and goals. The confluence of this information at the level of the VTA would control the DA input to the hippocampus and thereby enhance the entry of the information into memory.

Summary, Predictions, and Implications

In summary, the evidence we have reviewed points to the existence of a functionally important loop between the hippocampus and the VTA. The downward arc of this loop carries novelty signals from the hippocampus to the VTA where it stimulates the novelty-dependent firing of these cells. The evidence for this is quite strong; VTA activation is blocked by TTX application to subiculum and can be mimicked by exciting the subiculum. The synaptic and biophysical events at the VTA that trigger novelty-dependent burst firing are beginning to be understood.

In the upward arm of the hippocampal-VTA loop, the dopamine that is released enhances LTP. This enhancement has been clearly demonstrated in CA1, but it does not occur at the cortical synapses onto dentate granule cells. DA action is thus selective for particular hippocampal synapses and it will be important to survey more hippocampal regions to delineate the sites of DA action. Although there are strong indications that interfering with the DA system can affect memory itself (Figure 3B), the experiments do not yet clearly establish whether the DA target is the hippocampal CA1 region where the effects on LTP have been established (Figures 3 and 4).

Many of the key experiments that we have cited use a novel environment as a stimulus for evoking dopamine release and enhancing LTP (Figure 4). The positive aspect of such protocols is that there can be little doubt of the behavioral significance of the effects. The negative aspect is that the time scale of the stimuli and the resulting response is slow (minutes). This makes it difficult to identify the relevant neural signals and to follow them around the loop. What is now needed is the development of behavioral paradigms that allow the rapid presentation of novel stimuli; this will make it possible to determine whether these stimuli elicit short-latency responses. This should allow the detection of real-time single-unit responses in the hippocampus that reflect the novelty detection process. Experiments of this kind would make it possible to localize the site of novelty detection in the hippocampus. A key prediction is that these responses will precede the novelty responses in the VTA.

The ability to detect novelty signals would make it possible to examine the type of neuronal responses that represent novelty under different conditions. There are likely to be several different forms of novelty. For example, one form of novelty may relate to events that are unexpected under a given cue condition; other forms of novelty occur when the stimulus has literally never been seen before or never been seen in a particular configuration with other stimuli (associative novelty). Thus, just as there are various forms of memory within specialized subregions of the temporal lobe (Brown and Aggleton, 2001), there are likely to be a range of novelty signals that are relevant under particular conditions. The ability to observe such novelty signals in real time will help to trace these signals to their source.

We suspect that an ultimate function of the hippocampal-VTA loop relates to the need to protect previously stored information. Because synaptic modification is set in motion by neuronal activity, there is the potential that activation of this network under any condition may overwrite stored information. Such activity might include use of the network to recall stored information or simply the processing of spontaneous noise, conditions that do not require plasticity. The role of the dopamine system may be to ensure that long-term plasticity cannot occur unless it is behaviorally advantageous; without dopamine, late LTP does not occur and early LTP decays within about an hour. The complexity of the downward arc of the loop may be designed to precisely determine the conditions under which long-term modification is allowed. The function of the novelty detection process itself is to perform a network-wide decision regarding whether the incoming information is truly new or just a degraded representation of a stored memory. However, as we emphasized before, even if the information is new, activation of the VTA appears to be contingent on additional criteria, notably relevance to goals and salience. In this way, the system only allows late LTP during restricted periods, thereby minimizing the possibility of overwriting previously stored information. Molecular or lesion methods need to be developed that will interfere with the flow of information around the loop; we predict that late LTP and learning would be dramatically reduced in such an open loop condition. Conversely, procedures that fixed the loop into a continuously functional (closed) condition would be expected to produce experience-dependent degradation of old memories.

The idea that the hippocampus and VTA act as a dynamical loop has several implications. First, the bidirectional flow between the hippocampus and VTA creates problems in separating cause and effect. For instance, fMRI signals generated in response to novelty have been interpreted as novelty detection, but given the rapidity of novelty detection as determined by other methods (e.g., Figure 1A), it is possible that the observed signals are a response of the hippocampus to novelty-dependent activation of the VTA and other neuromodulatory systems.

Loop dynamics could be important in disorders related to detection and selective attention to behaviorally relevant stimuli, such as schizophrenia (Lisman and Otmakhova, 2001), a disease in which the hippocampus and a hyperdopaminergic state have been previously implicated (reviewed in Heckers, 2004). This disease affects novelty signals, leading to abnormalities in latent inhibition and attention (Gray, 1998). A hyperdopaminergic state may interfere with novelty de-

tection because dopamine (through both D1 and D2 action) selectively reduces the EPSP generated by the cortical input to CA1 (Otmakhova and Lisman, 1999). Similarly, NMDA hypofunction, which is also implicated in schizophrenia (Coyle et al., 2003), would be expected to reduce more strongly the EPSP generated by the cortical input than that generated by the CA3 input (Otmakhova and Lisman, 1999). The selective reduction of the cortical input could then interfere with the comparator function by preventing the matching of predicted information arriving from CA3 with the cortical input that represents sensory reality (Vinogradova, 1984) (matching requires that both input pathways be functional). Since the resulting mismatch (novelty) signal would stimulate more dopamine release and because dopamine would further reduce the cortical input to CA1, there is the danger of positive feedback in the loop. By blocking hippocampal-dependent activation of DA neurons (Grace et al., 1997; Otmakhova and Lisman, 1999), one of the functions of antipsychotic drugs (which are DA antagonists) could be to break the positive feedback in the loop.

In summary, we hope that this review will promote further study of the relationship between the hippocampus and the dopamine system. This has been an understudied area, but warrants more extensive study for several reasons. First, the hippocampal-VTA loop may regulate the flow of information into long-term memory and thus be a critical component of the brain's memory system. Second, understanding the loop is likely to provide insight into mental disease, most notably schizophrenia. Finally, the findings that normal variation in human memory can be linked to variation in the dopamine-degrading enzyme COMT and that memory can be enhanced by L-DOPA suggest that understanding dopamine action will provide methods for enhancing human memory.

Acknowledgments

This work has been supported by NIH grants and a NARSAD Distinguished Investigator Award. We thank Nonna Otmakhova for her help with the concepts developed in this paper and Charles Yang for his comments on the manuscript. We also gratefully acknowledge the support of the W.M. Keck Foundation.

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