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CHAPTER 32

The dentate gyrus as a filter or gate: a look back and a look ahead

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Abstract: The idea of the dentate gyrus as a gate or filter at the entrance to the hippocampus, blocking or filtering incoming excitation from the entorhinal cortex, has been an intriguing one. Here we review the historical development of the idea, and discuss whether it may be possible to be more specific in defining this gate. We propose that dentate function can be understood within a context of Hebbian association and competition: hilar mossy cells help the dentate granule cells to recognize incoming entorhinal patterns of activity (Hebbian association), after which patterns that are consistently and repetitively presented to the dentate gyrus are passed through, while random, more transient patterns are blocked (non-associative Hebbian competition). Translamellar inhibition as well as translamellar potentiation can be understood in this context. The dentate-hilar complex thus plays the role of a ''pattern excluder'', not a pattern completer. The unique role of pattern exclusion may explain the peculiar qualities of dentate granule cells and hilar mossy cells.

Keywords: dentate gate; dentate filter; pattern excluder

Introduction

The dentate gyrus, sitting between the entorhinal cortex and area CA3, is both anatomically well positioned and physiologically predisposed to play the role of a gate, blocking or filtering excitatory activity from the entorhinal cortex and controlling the amount of excitation that gets through to the hippocampus. Normal adult granule cells rarely generate action potentials. In part this is because there is little direct interconnectivity between dentate granule cells under normal conditions (reviewed in Chapter 1 of this volume). In addition, granule cells have a high resting membrane potential (Fricke and Prince, 1984; Scharfman, 1992; Staley et al., 1992; Williamson et al., 1993), and strong GABA receptor-mediated inhibition (Mody et al., 1992; Coulter, 1999; Nusser and Mody, 2002; Stell and Mody, 2002; Cohen et al., 2003; Mody, 2005).

History of the idea

Data that the dentate gyrus may serve as a gate appeared in at least as early as 1966 in work by Andersen et al. (1966). In these experiments, the hippocampal formation of adult rabbits was exposed by removal of the overlying neocortex and corpus callosum. Stimulating electrodes were placed into entorhinal cortex or in the perforant pathway. Extracellular as well as intracellular recordings were made from electrodes placed in the

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transverse plane of the hippocampus, piercing CA1 and both blades of the dentate gyrus. Perforant pathway stimulation resulted in a negative wave reflecting granule cell excitatory postsynaptic potentials (EPSPs) generated in the middle third of the dentate gyrus molecular layer. The EPSP was followed by a large and slow inhibitory postsynaptic potential (IPSP), persisting for 100–150 ms.

That EPSPs were followed by IPSPs persisting for 100–150 ms suggested that perforant pathway stimulation at frequencies higher than 10 Hz should result in a decremental granule cell population spike response (habituation). For pulse stimulus durations of less than 1 s, this decremental response was indeed observed. However, for longer pulse durations of 6 and 9 s, there was a gradual incremental granule cell response (facilitation), beginning after a few seconds of repetitive stimulation. The degree of facilitation increased with increasing stimulation frequency up to a maximum of 10 Hz, and was abolished by a stimulation frequency higher than 20 Hz (Andersen et al., 1966). Although not stated explicitly by the authors, these experiments established one way that the dentate gyrus appears to act as a gate. Short-duration stimuli carried at a certain frequency are blocked, but longer duration stimuli carried at the same frequency are facilitated. Later studies demonstrated additional ways the dentate gyrus acts as a gate.

In 1976, Alger and Teyler applied repetitive perforant pathway stimulation to rat hippocampal slices at 1 Hz for a total duration of 10 s (Alger and Teyler, 1976; Teyler and Alger, 1976). They found an incremental EPSP and population spike response with each succeeding stimulus (facilitation) in CA3 and CA1 but a decremental response (habituation) in the dentate gyrus. In contrast, stimulation of the perforant pathway at 15 Hz for 15 s produced potentiation of EPSP and population spike responses of dentate gyrus, CA3 and CA1. These results are similar to those of Andersen et al. (1966), showing that the dentate gyrus suppresses flow of excitation from perforant pathway input but that this suppression can be reversed with longer duration stimuli in an appropriate frequency range.

Winson and Abzug (1977, 1978) placed stimulating electrodes into the angular bundle of the perforant pathway in behaving rats, and compared dentate granular layer population spike amplitudes and molecular layer EPSPs in slow wave and rapid eye movement (REM) sleep vs. the alert and still state. The authors found that slow wave and REM sleep states are associated with larger population spikes but smaller EPSPs compared to the still, alert state. To explain these findings, the authors hypothesized that there was relative hyperpolarization of the dentate granule cell membrane potential during the still, alert state compared to slow-wave sleep. The relative hyperpolarization was interpreted as a gating mechanism.

Collins et al. (1983) studied the role of the dentate gyrus in seizure propagation in behaving rats. Stimulation with either focal chemoconvulsant injection into or electrical stimulation of entorhinal cortex produced a graded response. If focal chemoconvulsant injection induced fewer than 10 spikes per minute in entorhinal cortex, no or minimal behavioral changes were noted, and no metabolic changes were noted on later sectioning and deoxyglucose autoradiography. If 10–30 spikes per minute are induced in entorhinal cortex, then there is increased deoxyglucose uptake in the entorhinal cortex and in the dentate gyrus, but restricted in dentate gyrus to the molecular layer. Behaviors associated with weak seizure activity were observed. However, if greater than 40 spikes per minute were induced, moderate seizures developed. Metabolic changes then spread to the entire dentate gyrus, areas CA3 and CA1, the septal nucleus, and occasionally to the amygdala, nucleus accumbens, and ventral pallidum-lateral preoptic area. Spread to the contralateral side also occurred. Because metabolic changes were initially restricted to the molecular layer of the dentate gyrus, and only with further increases of chemical or electrical stimulation were these changes able to spread to other parts of the hippocampus and to extrahippocampal structures, the authors concluded that "the sequential changes in [deoxyglucose] metabolism suggest that the dentate gyrus acts as a restrictive gateway for seizure spread from entorhinal cortex to the rest of the limbic system…." (Collins et al., 1983).

Further work by Lothman and coworkers was reviewed in 1992 (Lothman et al., 1992). Working

in vivo with unanesthetized rats, Stringer et al. (1989) and Stringer and Lothman (1992) developed the concept of maximal dentate activation (MDA). Their experiments involved stimulation of the perforant pathway or area CA3 until a maximal, apparently saturating level of activity was recorded in the dentate gyrus. This state was defined as MDA. MDA was most easily obtained with a stimulating frequency between 10–40 Hz. The onset of MDA occurred with a pronounced negative shift of the DC potential, reflecting a depolarization of the granule cell layer. In addition, there was an abrupt rise in extracellular K^+ concentration, and the appearance of bursts of large amplitude population spikes. If stimulation was triggered above the threshold for MDA, afterdischarges were observed, which could persist for a short time after stimulation ceased. MDA in the intact rat was always bilateral and associated with synchronous epileptiform discharges in bilateral CA3, CA1, subiculum, and entorhinal cortex. Lesioning the entorhinal cortex on one side can block MDA on that side, but the contralateral side retained the ability to reach MDA. If stimulation were applied to the perforant pathway, MDA occurred in the dentate gyrus before activity was recorded in CA1. Thus, it appeared that transmission flowed from entorhinal cortex to dentate gyrus to CA3 and CA1, and not by the direct entorhinal to CA1 (temporoammonic) pathway.

Lothman et al. (1992) and Stringer and Lothman (1992) interpreted their data in the following way: "(1) MDA serves to initiate and sustain reverberatory seizure activity in [the] hippocampal–parahippocampal loop; (2) this reverberatory seizure activity bombards extrahippocampal structures; (3) MDA can directly (within the hippocampal–parahippocampal loop) and indirectly (by influencing sites outside the hippocampal–parahippocampal loop) modulate the length of electrographic seizures and, in turn, their propagation, thereby affecting the expression of various types of behavioral seizures; (4) MDA can be accessed from any point *within* the hippocampal–parahippocampal loop; (5) MDA can also be accessed from points *outside* this loop....". Thus the dentate gyrus, when its function as a control point is breached, actually acts as a "promoter" or "amplifier" of seizural discharges.

Walther et al. (1986) studied rat brain slices in superfusate containing a low concentration of magnesium, which was shown to induce repetitive burst discharges in their slices. The entorhinal cortex demonstrated prolonged epilepiform discharges, lasting minutes at a time. The subiculum was also capable of spontaneous discharges, lasting up to 9 s. In contrast, isolated minislices of area CA3 were only capable of brief spontaneous transients, and the dentate gyrus demonstrated no activity at all when connections to the entorhinal cortex were disrupted. Because even prolonged epileptiform discharges in the entorhinal cortex elicited only brief transient activity in the dentate gyrus, the authors suggested that "the dentate gyrus … may serve as a filter which reduces the excitatory load into CA3 and hence into CA1" (Walther et al., 1986). Further details of the pharmacology and electrophysiology of these slices were reviewed in Heinemann et al. (1992).

A striking visual demonstration of dentate gating was presented by Iijima et al. (1996) using optical imaging with fluorescence voltage-sensitive dye in rat brain slices. After superfusing their slices with an antagonist of GABA-A receptors, electrical stimulation in the superficial layers of the entorhinal cortex led to signals reflecting robust excitation of the entorhinal cortex. This first spread throughout the superficial layers of the entorhinal cortex, then involved the deep layers. At 33.6 ms after stimulation, excitation invaded the hippocampus, lasting until 151.2 ms after stimulation. The entorhinal cortex remained active through this time, and activity reverberated within the entorhinal cortex for the next 200 ms. In this period, the hippocampus showed only weak and partial activation. A second stimulus, delivered 352.8 ms after the first, caused further reverberatory activity in the entorhinal cortex, which then again penetrated to the hippocampus and led to hippocampal excitation lasting about 70 ms. A second experiment was also performed in normal solution (without the GABA-A receptor antagonist), using 1 Hz repetitive stimulation instead of single stimuli. Each stimulation resulted in increased activity in the entorhinal cortex, but it

was not until the seventh stimulus that activity penetrated to the hippocampus. These results demonstrated that entorhinal cortex activation, even when robust, does not easily penetrate into the hippocampus, presumably due to gating at the level of the entrance to the hippocampus, i.e., at the dentate gyrus.

Behr et al. (1998) used kindled animals to demonstrate the dentate gate and its "breakdown". The authors first superfused entorhinal-hippocampal brain slices in low-magnesium solution. Spontaneous seizure-like activity in both entorhinal cortex and in area CA3 was then recorded, but activity was significantly larger in amplitude and longer in duration in area CA3 of kindled slices compared to control slices. Transecting the perforant pathway greatly diminished epileptiform activity in area CA3, but transecting the subiculum-to-entorhinal pathway did not. These results demonstrated that epileptiform activity can be passed from entorhinal cortex through the dentate gyrus into area CA3, and that passage is made more likely after kindling. The authors then devised an experiment so that only the entorhinal cortex was locally perfused with both a GABA-A receptor antagonist and elevated K^+ to induce epileptiform activity in a spatially-specific manner. Electrical stimulation of the entorhinal cortex resulted in a much stronger response in the dentate gyrus of kindled slices. Furthermore, in a separate experiment, spontaneous entorhinal interictal activity failed to trigger epileptiform discharges in dentate gyrus in 8 out of 8 control slices, but did trigger them in 7 out of 9 kindled slices. Taken together, these results show that, in normal brain, the dentate gyrus appears to prevent epileptiform activity in the entorhinal cortex from reaching the hippocampus, but after epileptogenesis (exemplified by kindling), the dentate gyrus no longer functions as a gate.

Evidence for dentate gating of seizures was also found by monitoring the level of c-fos protein expression after the development of spontaneous seizures in a pilocarpine model of epilepsy in mice (Peng and Houser, 2005). The expression of c-fos protein is a marker for neuronal activity. Increased c-fos protein levels are evident 20–40 min after *c-fos* activation, at least in many neuronal types where it has been studied. At 15 min after a 1–2 min spontaneous behavioral seizure in epileptic mice, c-fos labeling appeared in dentate granule cells, spread throughout the entire extent of the dentate gyrus but not involving the interneurons of the dentate-hilar border or the dentate molecular layer. At 30 min, c-fos staining was intense in the dentate gyrus, involving both granule cells and dentate-hilar border interneurons, and increased c-fos staining also spread to the rest of the hippocampus. At 1–2 h, c-fos staining began to fade in the dentate granule cells but was intense in interneurons of the dentate-hilar border and the dentate molecular layer. At 4 h, c-fos staining was lighter throughout the hippocampus, including the dentate gyrus, compared to controls. These data suggested that dentate granule cell activation was likely to have been an early event in spontaneous seizures. The authors commented that the rate of c-fos expression varies between cell types, so that c-fos expression occurred first in dentate granule cells and later in dentate interneurons is suggestive, but not proof that activity in granule cells preceded that in dentate interneurons.

The breakdown of dentate gating and its presumed relationship to epileptogenesis motivated much of the research described above, at least as early as the work by Collins et al. (1983). It was recognized that the dentate gyrus is normally resistant to the propagation of discharges from the entorhinal cortex. In the setting of limbic epilepsy (i.e., temporal lobe epilepsy), the gate is thought to be compromised, so that seizure activity from entorhinal cortex is allowed into the hippocampus, and propagated in a reverberatory cycle back to entorhinal cortex again (Stringer and Lothman, 1992). This suggestion has led to many studies, which have focused on reasons why the dentate gyrus gate may "breakdown" in temporal lobe epilepsy. Based primarily on animal models of temporal lobe epilepsy, the results have suggested that the dentate gyrus gate may breakdown because of a change in the balance of excitation and inhibition of dentate gyrus granule cells. Decreased inhibition of granule cells could develop because of seizure-induced loss of GABAergic neurons or altered expression of $GABA_A$ receptors, among many other reasons (Mody et al.,

1992; Mody, 2005). Increased excitation may develop because of mossy fiber sprouting, as well as other factors (Stringer and Lothman, 1992; Sutula et al., 1992; Jackson and Scharfman, 1996; Scharfman, 2004). A more complex interplay between initial hyperexcitability followed by chronic hyperinhibition has also been suggested (Sloviter et al., 2006).

The idea of dentate gate vs. filter

In summary, there is now a series of studies, which suggest that activity in the entorhinal cortex is often halted, delayed, or diminished at the dentate gyrus. The decreased excitability appears to be related at least in part to the strong, prolonged dentate granule cell IPSP first described by Andersen et al. (1966). Further, as also found in that study, repetitive perforant pathway stimulation for a prolonged period of time (a few seconds or longer) results in facilitation of succeeding stimulations. Thus if the dentate gyrus is a gate, it is a gate that can be opened if one is persistent, i.e., if one keeps ''knocking'' on it.

Why does the dentate gate open with repeated stimulation? Meticulous simultaneous intracellular recordings seem to show that dentate and hilar interneurons respond strongly and faithfully to dentate granule cell discharges (Scharfman et al., 1990). However, with repeated granule cell discharge, the interneuronal response switch from action potentials to EPSPs — the interneurons still hear the command to fire but stop firing. Conversely, dentate and hilar interneuronal discharges produce IPSPs in dentate granule cells, but with many failures. Interestingly, failures are more likely after a large IPSP. These results suggest that at least part of the gating function resides in the local granule cell and interneuron circuitry, and that this inhibitory circuit is tuned down in efficacy with repeated activation (Scharfman et al., 1990).

Such *activity-dependent disinhibition*, involving principal neurons with their local interneuronal circuitry, appears to be an important recurring theme in other brain areas as well (Ben-Ari et al., 1980; Wong and Watkins, 1982; McCarren and Alger, 1985; Deisz and Prince, 1989; Thompson and Gahwiler, 1989a, b, c; Scanziani et al., 1991; Mott and Lewis, 1992; Thomson et al., 1993). For instance, in area CA3, repeated stimulation of pyramidal neurons leads to decreased IPSCs via two mechanisms: (a) prolonged activation of GABA-A receptors, which leads to a chloride influx into the principal neuron, which leads to a decrease in driving force for chloride-mediated GABAergic inhibition, and (b) presynaptic negative feedback of GABA onto GABA-B receptors, which leads to decreased presynaptic GABA release (Thompson and Gahwiler, 1989a, b, c). Further details on complex GABAergic responses have been studied and reviewed (Kaila, 1994; Kaila et al., 1997; Staley, 2004).

Given that the dentate gyrus can function as a gate, is there also a way in which the dentate gyrus might act as a filter? The prolonged IPSP in effect acts as a high-frequency filter, but is there a more specific way in which the dentate gyrus might act as a filter of *information*? We would like to suggest that the dentate gyrus does indeed filter information in a specific way. We prepare for discussion of dentate filtering function with the following comments on hippocampal anatomy, mossy cell function, the relation of translamellar inhibition and potentiation to associative Hebbian learning, and the role of synaptic scaling in non-associative Hebbian competition.

A detailed review of hippocampal anatomy appears in other chapters of this volume. We note here only that the hippocampus has a striking lamellar structure, with the projections of the perforant pathway, the mossy fibers, the Schaffer collaterals and the alvear pathway, all appearing to be on nearly a plane (''lamella'') perpendicular to the longitudinal axis of the hippocampus (Andersen et al., 1969, 1971; Amaral and Witter, 1989). A point to be emphasized here for the discussion below is that hilar mossy cells project maximally onto granule cells that are septally and temporally displaced from the mossy cells of origin, not onto the granule cells from which the mossy cells receive input. That is, mossy cells projections are unique in being preferentially *perpendicular* to the plane of the lamellae (Amaral and Witter, 1989).

Why do mossy cells project in this way? A detailed discussion of mossy cell function appears in a separate chapter of this volume. We summarize the principal features and suggest its role in dentate-hilar function as follows: (1) mossy cells can mediate both translamellar inhibition as well as potentiation; (2) translamellar potentiation as mediated by mossy cells is weak, and an individual mossy cell, by itself, cannot cause a dentate granule cell to discharge; (3) optimal potentiation of dentate granule cells requires near-simultaneous stimulation of both the perforant and association pathways (which we refer to as "double input"), to within a time interval on the order of about 5 ms. A caveat is that the functional width of a lamella at the level of the dentate gyrus may be as thick as 2.5 mm (Zappone and Sloviter, 2004).

We also propose that granule cells scale their activity to pass only the most favored or most potentiated dentate patterns. That is, individual granule cells evaluate not only whether individual synapses are favorable or not (the traditional, associative Hebbian LTP or LTD), but also whether the number of action potentials averaged over some period of time is too low or too high. If the average activity of one particular neuron is too low, all synaptic strengths of this neuron are scaled up; and if too high, all synaptic strengths are scaled down, so as to preserve the average activity within some characteristic range (LeMasson et al., 1993; Turrigiano and Nelson, 2000). Experimental evidence for this kind of activity-dependent homeostatic synaptic scaling in other brain areas exists (Royer and Pare, 2003; Wierenga et al., 2005). Hebbian systems that are not capable of similar homeostasis of activity evolve inevitably into a state of tonic hyperactivity or global silence (Miller, 1996, Marder and Prinz, 2002).

As a consequence of activity-dependent synaptic scaling, the establishment of potentiated input patterns causes the response of a neural system to non-potentiated patterns to be scaled down, even in the absence of specific LTD mechanisms for the non-potentiated patterns. That is, for synapses to survive in competition with other synapses, it is not enough that they not be specifically identified as being unfavorable; synapses will nonetheless be scaled down in strength if there are other synapses that are systematically scaled up or potentiated. We refer to synaptic scaling as being representative of a type of non-associative Hebbian competition.

Thus we suggest that translamellar potentiation be viewed in terms of Hebbian associative learning, with the additional twist that double input from both the perforant and associative pathways results in more effective potentiation. Indeed, input from only one source, e.g., the association pathway only, may actually result in depotentiation through Hebbian competition. To see this, consider repetitive perforant pathway input that arrives at dentate granule cells in a certain number of lamellae (Fig. 1). The dentate granule cells in these lamellae fire multiple action potentials. These granule cells cause mossy cells downstream in the same lamellae to fire multiple action potentials as well. These mossy cells then send signals to many other lamellae. Some of these other lamellae receive near-simultaneous perforant and association pathway input, and some do not. For lamellae that do receive near-simultaneous perforant and association pathway input, one expects the mossy

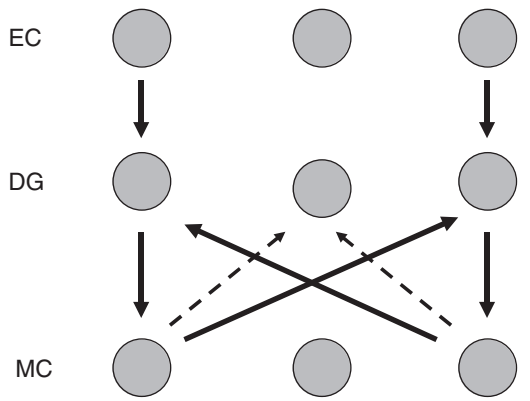

Fig. 1. Dentate-hilar potentiation is mediated by double input from both entorhinal cortex neurons and from hilar mossy cells. EC = entorhinal cortex; DG = dentate gyrus granule cells; MC = mossy cells of hilus. Repetitive stimulation of dentate granule cells by entorhinal cortex neurons causes transmission of excitation to mossy cells in the hilus. The mossy cells then stimulate extralamellar granule cells (plus interneurons near those granule cells). Those granule cells that receive input from both entorhinal cortex and from mossy cells become potentiated, while those that do not, become depotentiated. Potentiated connections are represented by thick arrows. Depotentiated connections are represented by dashed arrows.

cell-to-granule cell connection to be potentiated. However, Hebbian competition then requires that non-potentiated connections be scaled down in strength. Thus lamellae that do not receive simultaneous perforant and association pathway input will find their mossy cell input weakened.

What is the timescale for translamellar inhibition? A scaling mechanism should take place on a timescale that is much longer than the baseline dentate granule cell firing interval, because a scaling mechanism requires monitoring and averaging the firing rate over some period of time. One set of experiments (Zappone and Sloviter, 2004) found translamellar inhibition to appear on a timescale of 200 s. A timescale this long is consistent with a scaling mechanism, and is not consistent with direct connectivity-related effects (i.e., disynaptic mossy cell to basket cell to granule cell transmissions).

Translamellar potentiation and inhibition can now be put together in a consistent scheme for system learning. Translamellar potentiation allows associative learning, while translamellar inhibition helps maintain dynamical system stability. Consistently successful double input from both perforant and association pathways results in translamellar potentiation (Steward et al., 1977; Buzsaki and Eidelberg, 1982; Strowbridge et al., 1992; Hetherington et al., 1994; Strowbridge and Schwartzkroin, 1996; Kleschevnikov and Routtenberg, 2003), while multiple inputs from mossy cells without concomitant perforant pathway input result in translamellar inhibition (Zappone and Sloviter, 2004). Translamellar inhibition and potentiation are thus complementary mechanisms, both necessary for a stable system capable of continual learning.

Dentate-hilar filtering function: a hypothesis

Various ways in which mossy cells can help the dentate gyrus function as a filter have been proposed. Buckmaster and Schwartzkroin (1994) have suggested a granule cell association hypothesis, wherein the mossy cells help to link subpopulations of granule cells. They suggested that the dentate-hilar role is one of pattern recognition, where the role of the mossy cells is to fill in missing components of perforant pathway input. For example, if the dentate-hilar complex learns to recognize a pattern involving co-activation of granule cells in lamellae A, B, and C, but later receives perforant pathway input only at lamellae A and B, then the mossy cells via association pathway potentiation will nonetheless stimulate granule cells in lamella C to fire. This type of pattern recognition is often referred to as "pattern completion". It is tuned to be *sensitive but not specific*. The mossy cells will cause granule cell co-activation in a remembered pattern, if the input pattern is "close enough" to the remembered pattern. That mossy cell projections are perpendicular to the perforant pathway and project preferentially to distant granule cells, sets up an ideal geometry for the mossy cells to play an associative role. It was not clear to these authors why associations between distant granule cells should be mediated by a separate cell population (the mossy cells), but it was conjectured that this arrangement allowed for independent influences to act on granule cells and mossy cells separately, and that nearest-neighbor granule cell co-activations may be discouraged, thus preventing a dangerous accretion of co-localized excitation (Buckmaster and Schwartzkroin, 1994).

Alternatively, considering that granule cells are difficult to activate while mossy cells are easily activated, Jackson and Scharfman (1996) proposed that mossy cells act as a switch: "By keeping activity in the granule cells either above or below a threshold for potentiation of synapses on pyramidal cells, mossy cells could create a bistable system, and thus form a gate to control whether or not information will be stored in the downstream elements of the trisynaptic circuit". Other influences on the mossy cells could presumably determine whether the switch is turned on or off.

We offer yet another explanation of the dentate filter, closer to that of Buckmaster and Schwartzkroin (1994) but differing in an important way. Mossy cells can help bring granule cells closer to threshold but rarely trigger granule cell action potentials by themselves (Hetherington et al., 1994; Scharfman, 1995; Kleschevnikov and

Routtenberg, 2003). Such weak mossy cell association does not lend itself to high-sensitivity pattern recognition, as missing components of a perforant pathway pattern are not likely to be filled in by mossy cell collateral input. The finding that temporal to septal association is absent or very weak in rats (Hetherington et al., 1994) would also lead to very poor pattern completion capabilities, as essentially there is no pattern completion capability in the temporal to septal direction. Furthermore, association pathway potentiation, as discussed in the previous section, is best triggered with double input from both the perforant and association pathways (Fig. 1). Inconsistent pattern input may not simply be ignored, but may lead to loss of potentiation and possibly even inhibition of granule cell response. Thus, we agree that the dentate-hilar complex is a pattern recognition complex, but we propose that it represents an *unforgiving* pattern recognizer, one that is *specific but not necessarily sensitive*. We propose that the dentate-hilar complex is not a pattern completer, but a pattern excluder. Its job is to exclude input patterns that are not exactly right.

Dentate-hilar function, in our conjecture, thus consists of the following steps: (1) patterns are presented to the dentate-hilar complex via repetitive perforant pathway input, (2) mossy cells strengthen granule cell responses to patterns that are repeated in a consistent and persistent way (translamellar potentiation), and weaken random or erratically presented patterns (translamellar inhibition), (3) Hebbian competition, through non-associative mechanisms, scales granule cell firing thresholds to fire only with the most highly potentiated pattern or patterns, (4) with future repetitions, the most highly potentiated pattern or patterns are allowed to pass through, while more random patterns are blocked.

In this model, the dentate gyrus functions as both gate and filter. It is a gate that can be opened by persistent, repetitive stimulation, and it is a filter in that it prefers that the stimulation be consistent, in terms of the pattern of the stimulation as distributed along the longitudinal axis. That is, one must "knock" on the gate not only many times, but in nearly exactly the same way each time. Random knocks are ignored.

What is the optimal frequency for opening the dentate gate? Comparing repetitive stimulation at 0.5, 4, 7, 10, and 20 Hz, Andersen et al. (1966) found that 10 Hz was optimal. Comparing repetitive stimulation at 0.5, 5, and 100 Hz, Mott and Lewis (1992) found that 5 Hz was optimal. The frequencies 5–10 Hz fall in the theta–alpha band, which is known to be prominent in limbic structures including the hippocampus (Bland, 1986; Freund and Buzsaki, 1996; Buzsaki, 2002; Buzsaki et al., 2003). We therefore conjecture that theta oscillations indicate activity requiring opening of the dentate gate.

We comment that the dentate-hilar complex combines a sluggish but powerful excitatory source (the dentate granule cells) with a highly labile but weaker component (the mossy cells). The sluggishness of the granule cells and the weakness of mossy cell output allow the granule cells to maintain high specificity, but the lability of the mossy cells nonetheless allows highly responsive associative learning. This dual need for specificity and association may explain why dentate-hilar association is mediated by a specialized cell population (the mossy cells), while in CA3 and in the neocortex, association occurs directly between principal cells. The dentate-hilar complex is unique in being tuned for specificity.

A look ahead

Our conjecture for dentate-hilar function is speculative, but testable. The simplest type of experiment would be to monitor all EPSPs from the dentate granular layer in one lamella, and to calculate the initial slope of each EPSP, denoted E in units of volts per second. One would also keep track of which E's result in population spikes. Then a distribution function can be constructed, G(E), giving the probability of observing each value of E (Fig. 2, filled squares). One can also determine the threshold E_0, defined as the smallest E above which a population spike is likely (e.g., with a likelihood greater than 95%). Alternatively, one can define various threshold functions with parameters that can be extracted from experiment. For instance, one can hypothesize a threshold

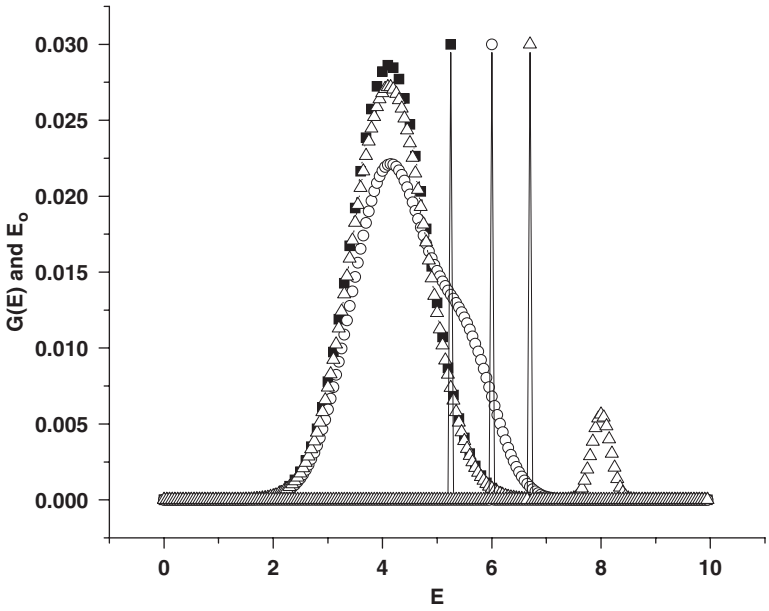

Fig. 2. Hypothetical distributions of $G(E)$ and E_0 with E in arbitrary units. Filled squares: baseline $G(E)$. The single solid square at $E = 5.28$ represents the threshold E_0 such that 95% of the distribution has $E < E_0$. Open triangles: hypothetical $G(E)$ after potentiation. The threshold is at $E = 6.72$. Open circles: hypothetical $G(E)$ in chronic epilepsy. The threshold is at $E = 6.00$.

function of the form

$$P(E) = A \exp(B(E - E_0)),$$

where $P(E)$ is the probability that a given E results in a population spike. Here A is a normalization constant, E_0 is the firing threshold for E, and B controls how sharp is the transition to firing. The parameters B and E_0 can be extracted from experiment, by plotting log $P(E)$ vs. E. The idea of an adjustable firing threshold E_0 is key to our model for dentate-hilar function.

What happens to $G(E)$ and E_0 after potentiation? If one stimulates the perforant pathway repetitively at a frequency f_S with a certain number of repetitions N_R, one expects potentiation of the dentate response to future stimulations. The ideal frequency for potentiation may be 5–10 Hz for 6–9 s (Andersen et al., 1966; Mott and Lewis, 1992), as discussed above. The relevant E to monitor may be the median or maximal value over the N_R repetitions. After potentiation, one may repeat the procedure for constructing $G(E)$, and see how this distribution function has changed. One may hypothesize that $G(E)$ develops a new peak at higher E, representing potentiated EPSPs, with threshold E_0 between this new peak and the old peak (Fig. 2, open triangles). EPSPs from the new high-E peak are passed by the dentate gyrus, while those from the old peak are blocked. The more distinct is this new peak, the easier it becomes to exclude incorrect patterns. Small fluctuations in the value of E_0 would not greatly affect specificity.

What happens to $G(E)$ and E_0 in chronic epilepsy? With loss of mossy cells, one might hypothesize that it becomes more difficult to create a distinct high-E peak. One might hypothesize, for instance, that only a high-E shoulder is created (Fig. 2, open circles). The function of the dentate-hilar complex as a pattern excluder would thus be degraded. The threshold E_0, furthermore, would have to be placed on a steeper part of the curve for $G(E)$. Any slight fluctuation of E_0 would cause dentate activity either to be overly inhibited (E_0 too high) or overly excitable (E_0 too low).

The effect of recurrent excitatory mossy fiber collaterals (reviewed in Chapter 29 by Sutula and Dudek in this volume) on $G(E)$ and E_0 should also be very interesting. One might expect either a

high-E shoulder or a separate higher-E peak, similar to that seen due to potentiation in the normal state discussed above. However, unlike the high-E contribution mediated by mossy cells, the high-E contribution from recurrent mossy fiber collaterals carries no useful information, because the associated EPSPs are the result of local recurrent excitations. Furthermore, if the high-E contributions from recurrent mossy fiber collaterals and from mossy cells overlap, then the filtering function of the dentate-hilar complex may be severely degraded.

A more ambitious experimental goal would be to determine the functional width of a lamella, and to develop techniques to stimulate and to record from individual lamellae reliably. This goal is likely to be technically challenging. The simplest alternative would be to place a single stimulating electrode into the angular bundle, one in each hemisphere, and a single recording electrode into the dentate granular layer, again one in each hemisphere. Presumably, one is guaranteed in this arrangement to have one pair of stimulating and recording electrodes in each of two distinct, nonoverlapping lamellae (one in each hemisphere).

However many distinct lamellae are accessible to experiment, one may then stimulate a subset of them simultaneously and repetitively, at a certain frequency of repetition for a certain number of repetitions, N_R. This frequency may again be taken in the range of 5–10 Hz (Andersen et al., 1966; Mott and Lewis, 1992). The spatial pattern of the stimuli represents the pattern to be learned. A distribution function $G(E)$ can then be constructed for this system, with one $G(E)$ for each lamella.

Of interest would be the number of repetitions, N_R, needed to teach a given target pattern, and whether the train of N_R repetitions need to be repeated a certain number of times. After potentiation of the target pattern is achieved, a test of sensitivity would be to present, simultaneously, the target spatial pattern plus a random pattern of variable amplitude, and then see if the random component is blocked while the target pattern is allowed through. A test of specificity would be to present only a part of the target spatial pattern, and see how close the presented pattern has to be to the target pattern to be passed through.

The stimulation strength necessary to produce EPSPs and population spikes is also of interest. One expects a threshold effect for the stimulation strength S (in units of volts), wherein a minimal value of this necessary before population spikes are seen. A distribution function can be defined, $D(E,S)$, giving the probability of observing a given E and S. It would be of interest to know what happens to $D(E,S)$, E_0 and S_0 after potentiation, and in the context of chronic epilepsy.

Finally, if it turns out to be true that the dentate-hilar complex is a pattern excluder, one may then employ similar arguments as developed in this chapter to speculate on the function of the auxiliary pathways, e.g., the direct pathways from entorhinal cortex to area CA3 (Hjorth-Simonsen and Jeune, 1972; Steward and Scoville, 1976; Witter and Amaral, 1991). One possible function for the auxiliary pathways may be to help validate signal passed into the hippocampus. We discuss this point at a little greater length below.

By the activity-dependent homeostasis hypothesis (LeMasson et al., 1993; Turrigiano and Nelson, 2000), all principal neurons have a preferred target firing rate, with homeostatic mechanisms to return to this rate over some period of time if perturbed away from it. If we assume that this hypothesis applies to granule cells, then there must be some rate at which granule cells fire action potentials spontaneously, even in the absence of perforant pathway stimulation. This rate is low but cannot be zero. How can CA3 principal neurons downstream from granule cells know if the signals they receive from granule cells are due to spontaneous granule cell activity or due to perforant pathway stimulated activity? There should be some way to ignore the inevitable (if rare) spontaneous granule cell discharge, while not compromising a faithful response to legitimate, stimulated granule cell discharge.

The answer may be that CA3 principal neurons have their own $G(E)$ distribution function, and they scale their firing thresholds to fire only with the most highly potentiated inputs. Thus if a set of CA3 principal neurons have been trained to expect "double input" from granule cells and from entorhinal neurons via the auxiliary entorhinal-to-CA3 pathway, then these CA3 principal neurons

are less likely to fire if they receive input only from granule cells. Thus, auxiliary pathways may play a crosschecking role, validating information arriving via the main pathways. If a confirmatory signal does not arrive via an auxiliary pathway, then information arriving via the main pathway may be ignored. The additional input from the auxiliary pathway may be needed to push a principal neuron above the firing threshold.

In summary, the current wealth of experimental data on the dentate gyrus shows that the dentate gyrus does function as a gate. We further conjecture that it also functions as a highly specific pattern recognizer, or filter. The data to date do not directly address this conjecture. We suggest future experiments that may help to prove or disprove the filtering conjecture. Even if the specifics of our conjecture are wrong, we hope these experiments will deepen our insight into the structure and function of the dentate gyrus and hippocampus.

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