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Review

Synaptic plasticity in early aging

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Abstract

Studies of how aging affects brain plasticity have largely focused on old animals. However, deterioration of memory begins well in advance of old age in animals, including humans; the present review is concerned with the possibility that changes in synaptic plasticity, as found in the long-term potentiation (LTP) effect, are responsible for this. Recent results indicate that impairments to LTP are in fact present by early middle age in rats but only in certain dendritic domains. The search for the origins of these early aging effects necessarily involves ongoing analyses of how LTP is induced, expressed, and stabilized. Such work points to the conclusion that cellular mechanisms responsible for LTP are redundant and modulated both positively and negatively by factors released during induction of potentiation. Tests for causes of the localized failure of LTP during early aging suggest that the problem lies in excessive activity of a negative modulator. The view of LTP as having redundant and modulated substrates also suggests a number of approaches for reversing age-related losses. Particular attention will be given to the idea that induction of brain-derived neurotrophic factor, an extremely potent positive modulator, can be used to provide long periods of normal plasticity with very brief pharmacological interventions. The review concludes with a consideration of how the selective, regional deficits in LTP found in early middle age might be related to the global phenomenon of brain aging.

Keywords: Middle-age; Long-term potentiation; Adenosine; Brain-derived neurotrophic factor; Hippocampus

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1. Introduction

Whether and to what degree deterioration of synaptic plasticity contributes to the memory problems that characterize aging is a long-standing issue in neurogerontology (Barnes, 2003). Growing evidence that long-term potentiation (LTP) is a substrate for memory has served to focus the question to a specific and easily studied form of plasticity. LTP is synapse specific, rapidly induced, and extremely persistent; these characteristics provide non-trivial explanations for the great capacity, rapid acquisition, and stability of memory. No neurobiological candidate other than LTP satisfies these requirements for an encoding mechanism. Beyond this, the potentiation effect has a deep relationship with rhythmic patterns of brain activity associated with learning (Larson et al., 1986) and has been shown to accompany the formation of specific memories (Roman et al., 1987). And, while the issue remains controversial, there is a large literature showing that manipulations that disrupt LTP also interfere with learning (Bliss et al., 2003). Given these multiple lines of evidence, it is reasonable to assume that age-related deficits in LTP would contribute to declines in memory performance.

Evidence for such deficits was first described more than 25 years ago (Barnes, 1979). While of great interest, these discoveries did not strongly influence ideas about cognitive declines in aging or lead to novel strategies for treating age-related cognitive impairments. There would seem to be two broad reasons for this. *First*, in the absence of cell biological explanations, it was not possible to integrate the LTP impairments into ongoing analyses of how aging affects the brain. *Second*, there was no evidence as to when the LTP deficits first appeared. This point is critical because memory problems emerge in life long before any evidence of broad deterioration of brain functioning (see below). LTP impairments in very old animals could be pre-morbid phenomena, and thus not necessarily relevant to the early appearing memory losses.

In the present review, we will argue that LTP deteriorates in a regionally selective manner during the transition from young adulthood to middle age, and thus well in advance of age-related pathophysiology. Losses in plasticity are, in other words, among the first signs of brain aging. Using new information about the cellular bases of LTP, we will then propose a specific hypothesis as to why the potentiation effect begins to fail so early in adult life, and offer suggestions for how to rescue it.

2. Plasticity in old age

Initial tests for LTP deficits in aged ($\geq$2-year-old) rats used acute hippocampal slices and found no evident age-related impairments in the Schaffer/commissural projections from field CA3 to CA1 (Landfield and Lynch, 1977; Landfield et al., 1978). This was unexpected because other complex physiological effects, including the capacity of synapses to follow high frequency afferent activity, were clearly impaired in the aged slices. However, chronic recording studies led to the important discovery that LTP in the perforant path projections to the dentate gyrus decays more quickly in the aged brain (Barnes, 1979). Subsequent work with slices identified deficits in the induction and/or expression of LTP in field CA1 (Deupree et al., 1993; Sankar et al., 2000) while others, in

agreement with the earlier studies, found no evidence for deficits in that region (Diana et al., 1994; Norris et al., 1996). It now appears that these discrepancies depend on the stimulation patterns used to induce potentiation (Moore et al., 1993; Lanahan et al., 1997; Watabe and O'Dell, 2003) and the extent to which the animals have learning problems (Tombaugh et al., 2002). A conclusion that can be drawn from this work is that the basic machinery for producing LTP remains intact into old age but is less likely to be engaged by patterns of afferent activity generated during normal behavior.

The above is a surprising conclusion. Given the long list of cellular processes that are negatively affected in old rats, LTP, with all of its requirements for multiple transmembrane receptors, numerous second messengers, structural proteins, etc. (see below), should be a prominent casualty of the aging process. Subsequent sections will offer a 'redundancy' hypothesis to account for its resiliency. First, though, we need to ask if failure of plasticity is an afterthought of aging, or is instead a primary (early) consequence of getting older.

3. Loss of synaptic plasticity in early middle age

Age-related losses in memory and LTP could, as suggested above, be consequences of a general deterioration in brain physiology that happens late in life. However, work on cohorts of human subjects for the third through ninth decades of life indicates that memory loss begins early in adulthood and then continues to worsen in an almost linear fashion, leading to a situation in which the magnitude of decline from 20 to 30 is about as great as that from 70 to 80 years of age (Park et al., 2002). That memory deteriorates during the course of normal aging comes as no surprise to middle-aged people, but that it begins so early and progresses so steadily is perhaps unexpected. While not widely appreciated, animals also undergo substantial memory losses by early middle age. Retention scores in some versions of the radial maze are notably better in rats at 3 months than at 14 months of age (Granger et al., 1996). Middle-aged monkeys are similarly impaired relative to young adults (Herndon et al., 1997; Sloane et al., 1997). Memory loss is thus an early manifestation of brain aging across the mammals. Is this also true of LTP? There appears to be no evidence for such effects in the Schaffer-commissural projections to the apical dendrites of field CA1 or in the perforant path connections to the dentate gyrus, the two test beds of LTP research. We recently carried out an explicit test for deficits in the conventional CA1/hippocampal slice preparation and found that the degree of stable potentiation produced by a train of theta burst stimulation (TBS) was no different in CA1 stratum (str.) radiatum of slices prepared from young adult (1–2 months) versus middle-aged (8–10 months) rats (Rex et al., 2005). Such results could simply indicate that LTP does not deteriorate by middle age and therefore memory impairments occurring in mid-adulthood are attributable to factors other than a loss of synaptic plasticity. But there is also the possibility that aging does not act in a regionally homogenous fashion, and that concentration on the two most convenient regions for electrophysiological analysis (i.e., str. radiatum of field CA1 and the perforant path termination in the dentate molecular layer) has placed research in two areas that happen to be relatively resistant to aging. We explored this in a modest way by examining the basal (rather than apical) dendrites of field CA1; the basal dendritic field (str. oriens) also receives Schaffer collateral afferents

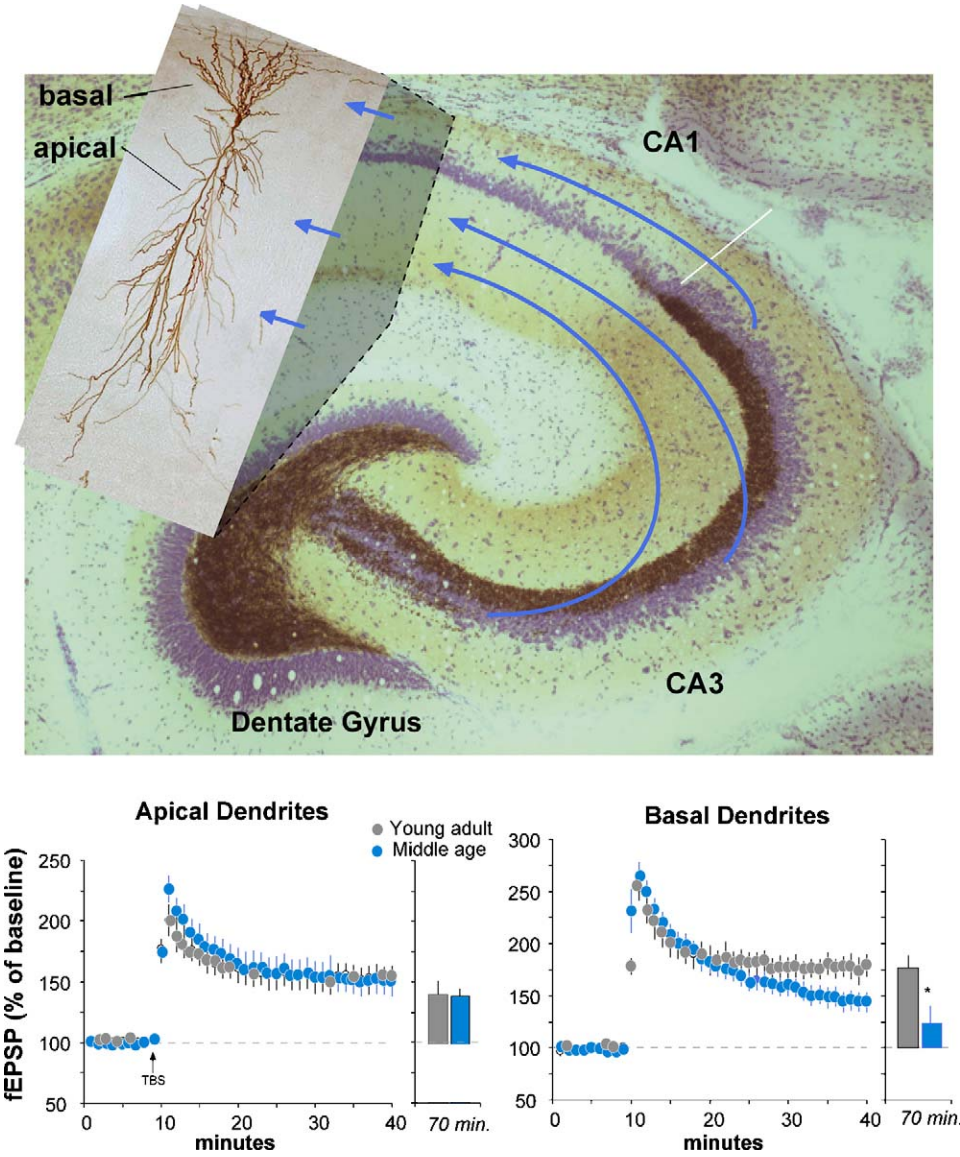

Fig. 1. Effects of aging on synaptic plasticity in the hippocampus. (Top) Shown is the disposition of connections between the two pyramidal cell fields of hippocampus. The zone of large pyramidal neurons (CA3) projects (the Schaffer-commissural fibers) in a laminar fashion to the region of smaller cells (CA1). That is, the portion of CA3 closest to the dentate gyrus innervates the more distal portion of the apical dendrite of the CA1 cell while that part of CA3 most distant from the dentate sends its axons to the basal dendrites. The inset shows a typical CA1 cell and where on its dendrites inputs from the subzones of CA3 terminate. (Bottom) Graphs summarizing the amount of LTP induced in the apical vs. basal dendrites of field CA1 by the delivery of theta burst stimulation to their respective CA3 projections. These experiments were carried out with slices prepared from 8 to 10 month (blue circles) or 2 to 3 month (gray circles) old rats. Note that potentiation in the apical dendrites (left side) is comparable in the young and middle-aged groups (indicated values are means ± S.E.Ms for groups of at least

(Amaral and Witter, 1995) but was not previously examined in neurogerontological studies. And, as shown in Fig. 1, LTP induced by theta burst stimulation in str. oriens is substantially impaired in slices prepared from 8 to 10 month old rats relative to that in slices from 2 month old animals. More specifically, while potentiation was about comparable in the two groups in the first several minutes following the stimulation train, it did not stabilize at above baseline values in the older slices.

The above results provide the first evidence that LTP deteriorates during the transition from young adulthood to early middle age, albeit in a regionally selective fashion. The results also reinforce a previous conclusion that plasticity of the basal dendritic synapses is significantly different than that in their apical counterparts. Earlier studies had shown that LTP has a lower threshold (requires fewer theta bursts) and is greater in magnitude in the basal than in the apical dendrites in field CA1 (Arai et al., 1994; Roth and Leung, 1995; Leung and Shen, 1999), an effect that can probably be attributed to regional differences in the incidence of potassium channels that mediate the after-hyperpolarizing potentials (AHPs) initiated by individual theta bursts (Arai and Lynch, 1992; Arai et al., 1994; Sah and Bekkers, 1996; Stackman et al., 2002). LTP also differs between the two dendritic domains with regard to the degree to which it stabilizes. Various experimental manipulations disrupt the stabilization of LTP in the apical dendritic field if applied immediately after TBS but become progressively less effective for disrupting potentiation over the following 30 min (Barrionuevo et al., 1980; Gall and Lynch, 2005 for a recent review). Thus, in the conventionally studied apical dendritic field, LTP passes through a memory-like consolidation period during which it becomes progressively more resistant to disturbance. This process is less effective in the basal dendrites in that reversal manipulations remain effective 30 min or longer after LTP induction. Indeed, it is conceivable that potentiation in the basal dendritic synapses never fully consolidates (Kramár and Lynch, 2003). The search for the origins of these apical/basal differences has focused on the integrins (Gall and Lynch, 2004, 2005) a family of transmembrane adhesion receptors that play a critical role in consolidating LTP. Immunocytochemical studies revealed that concentrations of at least some LTP-related integrins differ markedly between the two dendritic fields (Bi et al., 2001a; Chan et al., 2003). For example, as shown in Fig. 2, the apical processes have moderate to dense concentrations of immunoreactivity for α5 integrin (a component of the α5ß1 fibronectin receptor) while the basal dendrites do not. The unequal distribution of this integrin is also found in neocortical pyramidal cells, an observation that raises the possibility that differences in LTP consolidation, and in the differential effects of aging, occur throughout the cortical telencephalon.

What functional consequences could arise from the regionally selective, early onset of age-related changes in LTP? A reasonable place to begin answering this is with the related question of what two LTP variants on the same neuron adds to memory. Importantly, both dendritic fields receive their major innervation from the densely interconnected pyramidal cells of field CA3 (the Schaffer/commissural afferents) (Amaral and Witter, 1995). It is

seven slices). The bar graph to the right shows that this still holds for measurements collected 70 min after theta burst stimulation. In contrast, LTP in the basal dendrites (right side), though initially similar in the two groups, decays steadily towards baseline in the older slices. The difference between young adult and middle-aged groups is particularly evident at 70 min post-theta (right side) (graphs adapted from Rex et al., 2005).

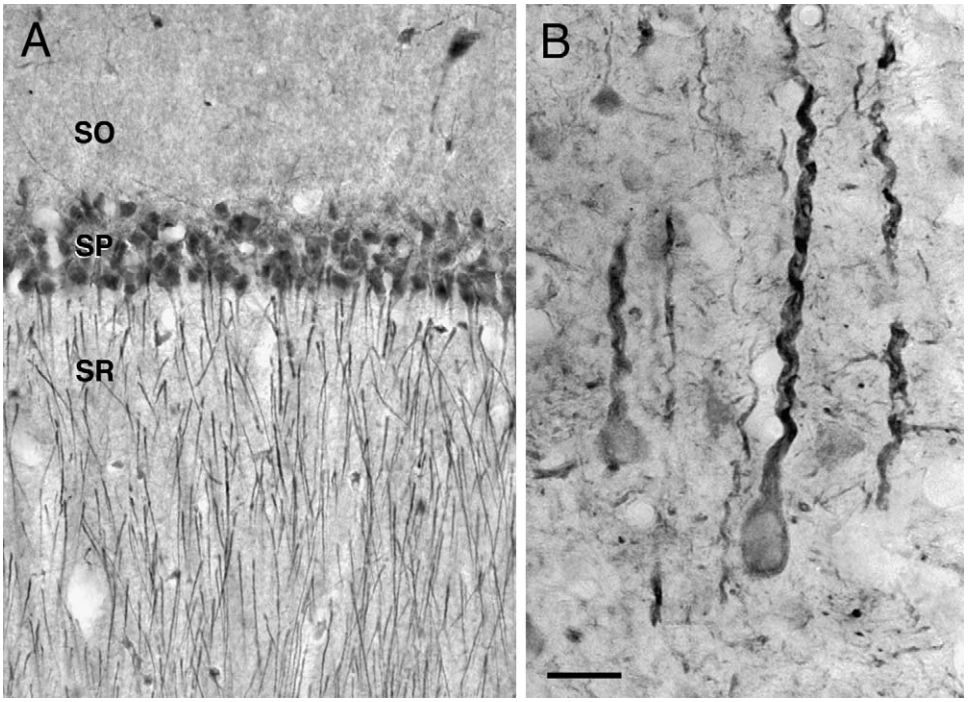

Fig. 2. Distribution of the α5 integrin subunit in hippocampal field CA1 is polarized. (A) Immunostaining for α5 integrin in hippocampal field CA1 shows that the protein is localized to somata in stratum pyramidale (SP) and apical dendrites in str. radiatum (SR) but is absent from the pyramidal cell basal dendrites that fill str. oriens (SO). (B) Photomicrograph showing that α5 immunoreactivity within neocortex is localized to cortical pyramidal cells, their apical dendrites, and scattered puncta in the neuropil; as in hippocampus, pyramidal cell basal dendrites are generally not labeled. Bar = 50 μm.

thus reasonable to assume that the two CA1 fields sample the same information. But, as noted regarding regional differences in the threshold to potentiation, that information is much more easily and potently encoded into LTP in the basal dendrites. These features result in a system containing components that (a) learn quickly versus gradually, and (b) encode memories at high versus moderate levels of strength. Importantly, memory in the first (rapid, basal) component appears to not consolidate while that in the second (gradual, apical) does, suggesting that the former, but not the latter, is unstable. Pertinent to this, the hippocampus and cortex have naturally occurring activity patterns that disrupt LTP (Wu et al., 2002; Colgin et al., 2004)—such patterns would only effectively erase *very recently encoded* potentiation in the apical dendrites but could erase LTP acquired over considerable periods in the basal dendrites. We propose that these erasure patterns operate as periodic 'sweeps' that eliminate relatively little from the one set of synapses (apical) and a great deal from the other (basal). An animal using this type of dual encoding would be free to acquire (through potentiation of low-threshold basal dendritic synapses) great masses of memory, some of which could prove to be useful in the succeeding minutes, while placing into long-term storage only those elements that re-occur and thereby cross

threshold for stable potentiation in the apical field. Animals would be 'Free' to initially acquire large volumes of information because the transient nature of the first type of memory insures that capacity issues will not arise. Dual encoding systems thus provide a partial solution to the problem of what to learn when not knowing what is important.

Based on the above arguments we would predict that memory losses with early aging will be greater for those forms of memory involving one time encounters with great masses of novel, undifferentiated material and relatively less for the acquisition of selected information for which repeated sampling or rehearsal is possible. The deficits found in the human life-span studies, as so far tested, do not involve long-term memory and therefore partly align with the first part of the prediction; similarly, evidence for impaired retention in middle-aged animals generally involves memories that ordinarily decay over hours or minutes. Explicit tests of the hypothesis would be better executed using tasks involving incidental learning, where cues are not explicitly identified as being significant, such as might be seen during exploration. That incremental encoding of stable memory will be relatively intact at least through early middle age – the second prediction of the model – appears not to have been tested, at least in animals.

Questions about functional significance lead naturally to the questions of why plasticity begins to deteriorate so early in adulthood and what might be done to rescue it. The following two sections begin this discussion with a survey of how LTP is produced and regulated.

4. The substrates of long-term potentiation

LTP production involves three stages – induction, expression, and consolidation – that will be discussed in order below.

4.1. Induction

Much of what we understand about induction is based on studies using theta burst stimulation (TBS) (Larson et al., 1986), a pattern of afferent activation modeled after physiological discharges observed during learning (Otto et al., 1991). Early work showed that theta stimulation (i.e., bursts of four 100 Hz pulses separated by 200 ms) is particularly well suited for inducing LTP, in that deviations from the pattern reduced the amount of stable potentiation. The reasons for the deep relationship between LTP and theta are summarized in Fig. 3. Shown are the responses of a cortical local circuit to two successive theta bursts. Note that the first burst induces a series of temporally summating EPSPs in the target cell but also triggers a feedforward IPSP that shunts the excitatory current. The net effect of this is that the depolarization from the burst does not achieve the magnitude and duration needed to unblock the voltage sensitive NMDA receptors that set the cascade leading to LTP in motion. The feedforward GABAergic IPSP is largely absent in the response to the second burst (Larson and Lynch, 1986), allowing for the serial EPSPs produced by the afferent burst to summate and engage the NMDA receptors. This refractoriness on the part of the feedforward event during the second burst is due to the activation, during the first burst, of GABA autoreceptors on the interneuron terminals that block release (Mott et al., 1990) (Fig. 3B). In addition to IPSPs, theta bursts activate

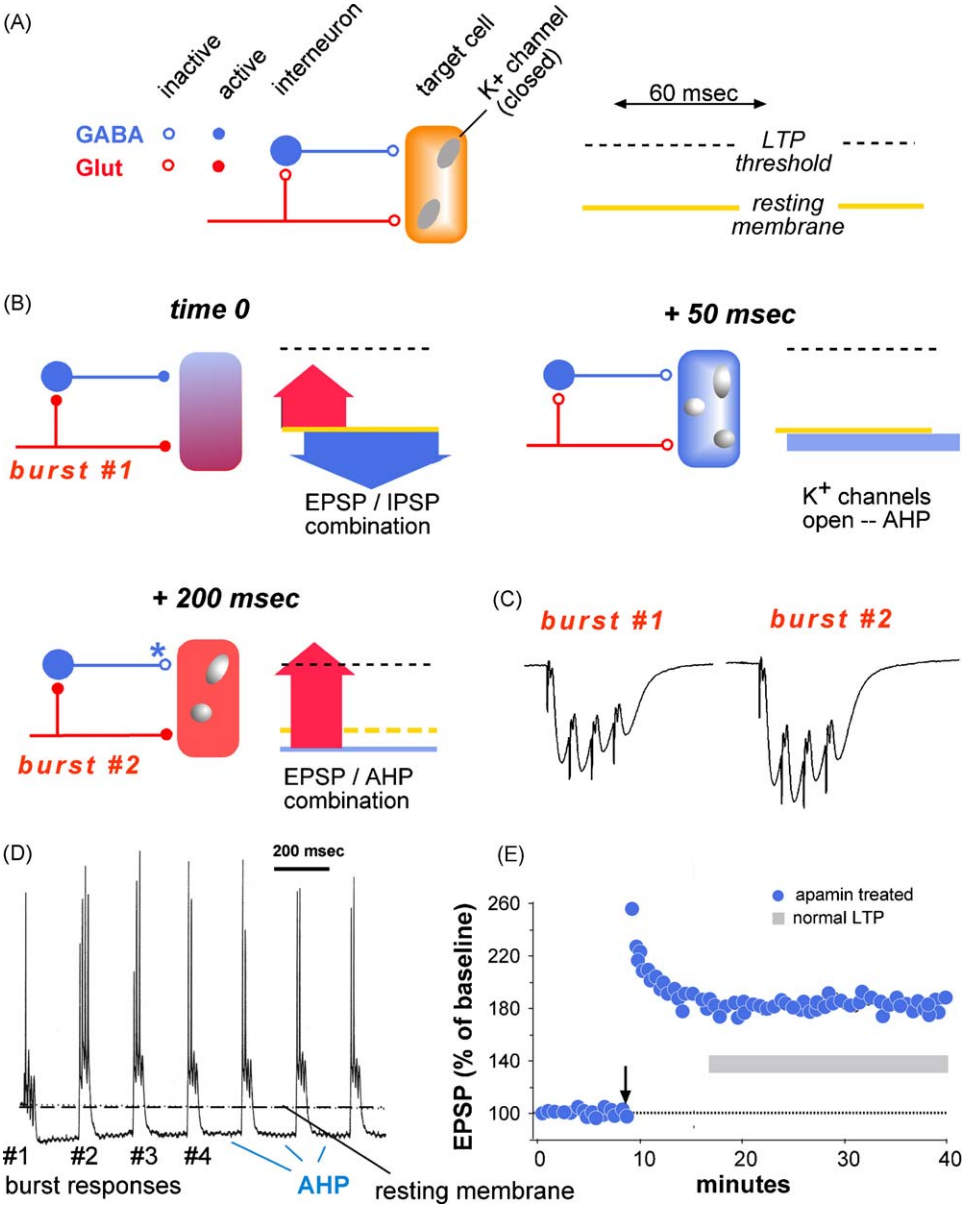

Fig. 3. Why theta burst stimulation effectively induces LTP. (A) A local circuit of the kind found throughout the cortical telencephalon. Three components are illustrated: (1) a glutamatergic input (red), (2) a feed forward GABAergic interneuron (blue), and (3) the target cell innervated by both. The membrane voltage in the target cell is shown schematically to the right; notably the baseline potential ('resting membrane') is not close to the value needed to remove the block on NMDA receptors and thereby set in motion the processes that result in LTP. The horizontal dimension signifies time. (B) Operation of the local circuit. Time 0 shows the events that transpire after the arrival of a theta burst (four action potentials in 30 ms) over the glutamatergic input. Initially this causes a pronounced depolarization of the target cell (indicated by red) but this is quickly counterbalanced by activation

voltage- and calcium-dependent potassium channels that generate AHPs lasting from tens of milliseconds to seconds (Stocker et al., 1999; Kramár et al., 2004). These AHPs, initiated by the early bursts, tend to reduce the depolarization associated with subsequent bursts. Fig. 3 illustrates the extent to which LTP is amplified when a subgroup of calcium-driven potassium channels that contribute to the AHP is blocked.

4.2. Expression

There is now broad agreement that changes in the number or operating properties of AMPA-type glutamate receptors are responsible for LTP expression. Probably the more parsimonious version of the hypothesis is that more receptors are added to the post-synaptic zone (Lynch and Baudry, 1988), and experiments by Malinow and colleagues have provided evidence in favor of this (Hayashi et al., 2000; Malinow and Malenka, 2002). How the increase is achieved is not at all clear. Most researchers probably favor a scenario in which NMDA receptor activation initiates machinery that inserts proteins into the membrane, or recruits receptors from extra-synaptic regions, making the increase in receptor number a primary effect (Passafaro et al., 2001; Bredt and Nicoll, 2003; Rouach et al., 2005). We prefer the original Lynch and Baudry proposal that changes in receptor number are secondary to changes in the size of the synaptic zone (the post synaptic density, psd), which themselves are secondary to alterations in spine morphology. The original impetus for this idea came from ultrastructural studies showing that shifts in spine and psd morphology accompany LTP (Lee et al., 1980), an observation subsequently greatly expanded by analyses with electron microscopic (Yuste and Bonhoeffer, 2001 for review) and newly developed light microscopic (Kramár et al., 2006; Lin et al., 2005) methods.

Morphological changes of this type would almost certainly require alterations to the spine cytoskeleton. Evidence for activity-induced effects of this kind was obtained initially in studies using dissociated cells (Fischer et al., 1998; Matus, 2000; Ackermann and Matus, 2003) and more recently with organotypic hippocampal slice cultures (Okamoto et al., 2004) and in vivo (Fukazawa et al., 2003). We recently developed an in situ labeling technique for visualizing F- (filamentous) actin within adult dendritic processes and spines (Lin et al., 2005). Using this, we found that theta stimulation triggers increases in F-actin in a subset of spines in the dendritic zone containing potentiated synapses (Fig. 4) and does so

(via a collateral of the input) of the GABAergic cell that imposes a hyperpolarization (blue) on the target cell. This slightly delayed, latter event prevents the membrane potential from moving to the level at which LTP can be triggered. Potassium channels begin opening 50 ms (+50 ms) after the first theta burst, resulting in an after-hyperpolarization (AHP) that moves the membrane potential still further from the value needed to induce LTP. A second theta burst arrives about 200 ms after the initial burst (+200 ms) and generates a response in the target cell that is depressed by the still present AHP. However, the input from the feedforward interneuron fails (asterisk), removing a countervailing influence to the response generated by the glutamatergic input. Absent this, the target cell response crosses the threshold for triggering LTP. (C) Extracellular responses to the first and second bursts in a theta train. The second composite response is about 50% larger than that to the first burst. (D) Typical example of how AHPs move the membrane potential away from levels at which LTP is induced. Note that the first burst is followed by an AHP that remains in place across succeeding burst responses. (E) The consequences for LTP of blocking a subset of potassium channels that contribute to the AHP. A theta train delivered under these circumstances generates about twice as much potentiation as would normally be the case.

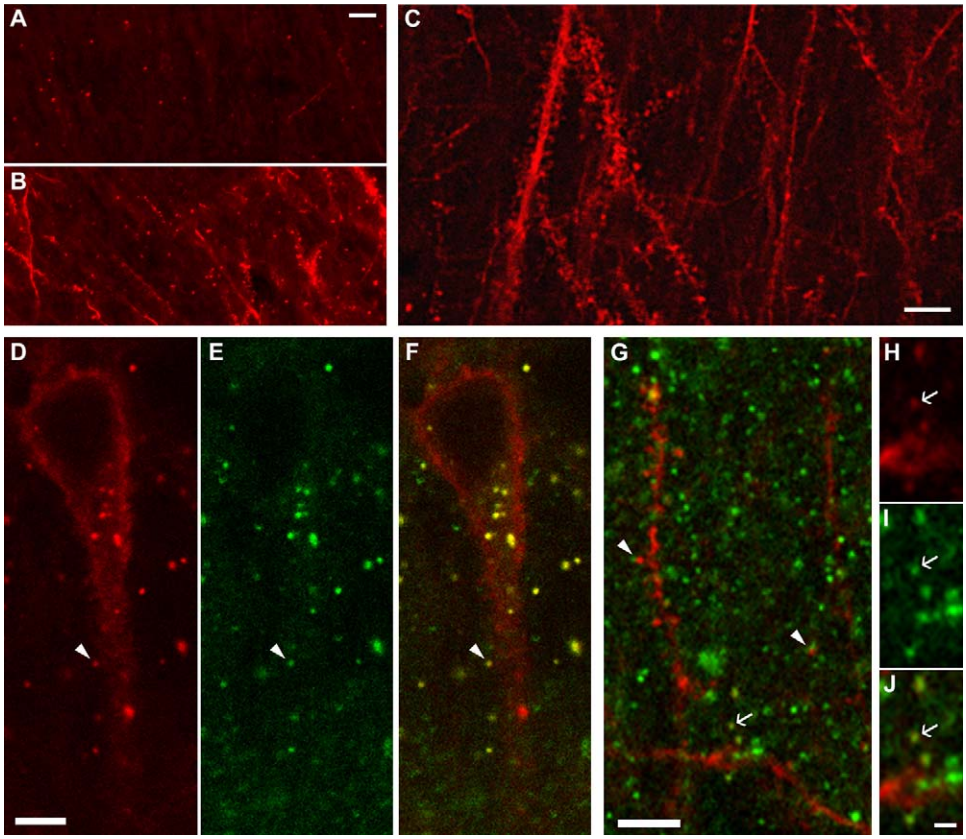

Fig. 4. Labeling of F-actin in an apical dendritic zone of field CA1 innervated by two stimulated populations of Schaffer-commissural fibers. (A–C) Phalloidin was topically applied to adult hippocampal slices for 20 min prior to delivery of stimulation pulses. Panels show epifluoresence photomicrographs of tissue receiving (A) single pulses at 0.03 Hz or (B, C) a train of 10 theta bursts. Theta stimulation induced a marked increase in labeling of spine heads. The continuity of labeling from dendrite to spine head is evident (arrows) in panel (C). (D–J) Laser scanning confocal images (single 1 μm optical slices) of fluorescent double-labeling in a dendritic field following the induction of LTP in its afferents. The in situ phalloidin labeling is seen as red fluorescence and immunolabeling of PSD-95, a synaptic scaffolding protein concentrated in spine heads, is seen as green fluorescence. (D–F) A series of images of a pyramidal cell photographed to reveal phalloidin labeling (D), PSD-95 immunoreactivity (E) and the combination of both (F: overlay image, double-labeling appears yellow). As shown, phalloidin densely co-labeled numerous PSD-95 puncta attached to the apical dendrite as well as in the surrounding field; certain of these can be seen to be spines associated with the faintly labeled apical dendrite (arrowhead). (G) Simultaneous phalloidin (red) and PSD-95 (green) labeling in another CA1 field. At this magnification some of the phalloidin-positive spines can seen to be ''capped'' with PSD-95 immunoreactivity (arrowheads). Panels (H), (I) and (J) show a subfield (of G) at higher magnification. The arrow points to a double labeled spine also found in panels (H–J). As is evident, this element and others lying above and below it are double labeled spines. Bar in $C = 10$ μm for (A) and (B), and 5 μm for (C). Bar in $D = 5$ μm for (D–F), in $G = 5$ μm for (G), in $H = 1$ μm for (H–J).

in under 2 min. The threshold (i.e., number of theta bursts) for producing this effect and for inducing LTP are very close and manipulations that disrupt consolidation also disrupt increases in spine F-actin (Kramár et al., 2006). While direct tests are still in progress, it is reasonable to assume that these changes to the actin cytoskeleton modify spine and psd morphology; given the multiple studies reporting that the number of AMPA receptors within synapses scales almost linearly with the size of the psd (Nusser et al., 1998; Takumi et al., 1999), such morphological changes would result in stable changes to the size of the excitatory postsynaptic currents generated by a constant release event.

The mechanisms through which theta stimulation and NMDA receptors initiate actin polymerization are still being worked out, but appear to depend upon ß1 family integrins (Kramár et al., 2006). This is not wholly unexpected because cytoskeletal regulation is a primary function of integrins across all types of cells (Zhu and Assoian, 1995; Geiger et al., 2002; DeMali et al., 2003) and there is compelling evidence that ß1 integrins regulate synaptic kinase signaling, the activities of synaptic NMDA receptors (Bernard-Trifilo et al., 2005), and processes critical for the stabilization of LTP (Chun et al., 2001; Kramár et al., 2002, 2006; Chan et al., 2003, 2006; Kramár and Lynch, 2003). Nevertheless, the new results obtained with the F-actin labeling method provide the first evidence that theta bursts engage the integrin-actin system in the adult nervous system.

4.3. Consolidation

Work with the in situ F-actin labeling technique showed that various manipulations reverse actin polymerization when applied immediately after theta stimulation but are without effect 30 min later (Kramár et al., 2006). This surprising correspondence with the time course of LTP consolidation is suggestive of a causal relationship, in which some set of events stabilizes newly assembled actin filaments and thereby stabilizes the new spine morphologies they support. The most likely candidate for a consolidation process of this type is cross-linking of the actin filaments, a function executed by a handful of proteins, the most prominent of which is spectrin (Goodman and Zagon, 1986; Fox et al., 1987; Bennett and Lambert, 1991) and its homologues. Spectrin is concentrated in adult brain membranes (Siman et al., 1987) and theta burst stimulation, applied at threshold levels for inducing LTP, causes its proteolysis (Vanderklish et al., 1995), evidently through activation of the calcium sensitive protease calpain (Bednarski et al., 1995; Vanderklish et al., 1995, 1996). These results point to a scenario wherein elevations in spine calcium levels, following upon theta-induced NMDA receptor activation, trigger calpain and thereby the disassembly of whatever cytoskeletal organization was present within the spine. New integrin engagement and signaling, also initiated by theta burst stimulation, would then set about reassembling and cross-linking the actin filaments, with the latter action constituting the true consolidation effect. Spectrin and other potential cross-linkers and anchoring proteins could be drawn down from extant pools, with final changes coming from newly synthesized replacement copies (Steward and Worley, 2002; Smart et al., 2003). Whether these events, occurring in the 30–60 min after LTP induction, are followed by even slower changes, as implied by reports that memory consolidation goes on for weeks or even longer, takes us beyond the known biology of small neuronal processes, and has to remain an intriguing subject for future research.

5. Redundancy and modulation in LTP

The conclusion that cytoskeletal rearrangements are central to expression and consolidation strongly suggests that redundancy is built into the machinery that produces LTP. There are many access routes to the machinery that regulates the cytoskeleton (Geiger et al., 2002; Ramakers, 2002; DeMali et al., 2003; Chen et al., 2006), presumably because reorganization is a fundamental step in so many basic cellular operations, and thus there is the possibility that failures in one of these links can be compensated for by altered activity in another. Such a system has a high probability of what might be called 'partial failures', in essence breakdowns that are present under one set of circumstances but not another. A good example of this is LTP in the aged brain: impairments are evident in aged rat hippocampus following theta pattern stimulation but not when long trains of high frequency stimulation are used (see above). Similarly, the LTP deficit in middle-aged hippocampus is partial, and can be overcome by various manipulations including greater than normal amounts of afferent stimulation (see below). Of course, redundancy and compensation will only rarely be perfect, so that the cytoskeletal changes and LTP rescued by them will not be exact copies of what would normally be present.

The many access routes to the cytoskeleton also means that there are multiple ways of modulating stimulus-driven changes in the actin network. It follows from this that there should be multiple, endogenous factors that positively or negatively affect the production of stable LTP. Recent work has confirmed this broad idea by identifying both positive and negative factors that modulate LTP under naturalistic circumstances. The neurotrophin brain-derived neurotrophic factor (BDNF) is the most potent facilitator of LTP yet discovered (Figurov et al., 1996; Akaneya et al., 1997; Kang et al., 1997; Bramham and Messaoudi, 2005). BDNF is synthesized by hippocampal and cortical pyramidal cells (among others), anterogradely transported to axon terminals (Altar et al., 1997; Conner et al., 1998), and released by theta burst stimulation (Balkowiec and Katz, 2000). After TBS-induced release, BDNF levels remain elevated in the extracellular space for about 10 min (Aicardi et al., 2004). Mature BDNF (mBDNF), at 2 nM concentrations, doubles the amount of LTP produced by a standard theta burst train and greatly reduces the number of bursts needed to produce a significant degree of stable potentiation (Kramár et al., 2004). Equally important, a fusion construct that scavenges endogenous (extracellular) mBDNF completely blocks the formation of stable LTP (Chen et al., 1999). As with some of the aging results, this suppression is only effective for theta-induced LTP—more intense stimulation with long, high-frequency trains ('tetanus') overrides the need for BDNF (Chen et al., 1999), a result indicating that this particular modulatory pathway is not the only route for reaching the LTP-associated cytoskeletal endpoints. Nonetheless, under naturalistic conditions the cascade set in motion by BDNF plays a vital role.

The presence of a potent negative modulator was indicated by the discovery that brief periods of hypoxia occurring immediately after theta stimulation completely eliminate LTP but are without effect 30 min later (Arai et al., 1990a). Hypoxia causes a massive release of adenosine into the extracellular space and antagonists of the adenosine A1 receptor prevented the disruption of LTP (Arai et al., 1990b). Moreover, adenosine infusion was as effective as hypoxia in producing a time-dependent block of LTP consolidation. Adenosine is released by bursts of afferent activity (Schubert et al., 1976; Dunwiddie and

Diao, 2000) and thus constitutes a second, negative modulator to go with the positive BDNF. How adenosine blocks LTP is not known but there are results suggesting that it regulates actin polymerization via effects on Rho GTPases (Rosso et al., 2002).

6. Causes of age-related changes in synaptic plasticity

From the above, we can specify five target categories for the effects of aging on LTP: induction, expression, consolidation, positive modulators, and negative modulators. In our studies demonstrating LTP impairments in middle-age, the theta burst responses used to induce LTP were not detectably different in slices from young adult and middle-aged rats, but the degree to which they facilitated within a theta train was greatly depressed in the latter group (Rex et al., 2005). Burst facilitation was fully restored by infusion of an adenosine A1 receptor antagonist. This suggests that adenosine release during initial bursts in the theta train reduced neurotransmitter release (via presynaptic A1 receptors) during subsequent theta bursts and thereby offset the response facilitation that normally occurs during the stimulation train. In any event, the altered burst facilitation does not appear to be responsible for the loss of LTP because it was of about the same magnitude in the apical and basal dendrites and, as described, deficits in LTP were not evident in the apical field. Moreover, there was no evidence for an age-related decline in potentiation obtained in the first few minutes following basal dendritic TBS, indicating that the bursts were suprathreshold for activating NMDA receptors and the machinery for LTP induction and expression.

Increasing the size of the theta burst responses, either by enhancing release or positively modulating post-synaptic glutamate receptors, restored LTP in the basal dendrites of middle-aged slices to young adult levels (Rex et al., 2005). This tells us that the mechanisms for consolidation (along with those for induction and expression of LTP) are intact in middle-aged slices, but that a partial failure has occurred in the pathways leading to them. As discussed, such breakdowns can arise from a defect in the redundant pathways themselves or from alterations in the signaling of positive and/or negative modulators. Tests of the latter possibilities have resulted in a candidate for the cause of the age-related loss of LTP.

As noted, adenosine is released by high frequency stimulation and potently blocks LTP consolidation. We tested if an exaggeration of this process disrupts LTP in middle-aged slices by applying an adenosine A1 receptor antagonist (DPCPX) to the slices 1–2 min after LTP was induced. With this protocol, the drug was not available to modify LTP induction and initial expression events but was present throughout the consolidation phase. The treatment proved sufficient to restore LTP almost to levels found in young adults (Rex et al., 2005). It appears then that the LTP problem in the basal dendrites arises from (i) an increase in adenosine release, (ii) a failure of adenosine clearance, or (iii) enhanced signaling through A1 receptors. A simple test of the clearance idea was carried out by measuring how much time was required for synaptic responses to recover from an infusion of high concentrations of adenosine (this depression arises from the above noted effect of pre-synaptic A1 receptors on release probability). As predicted if there were impairments to clearance, response recovery was slower in middle-aged than young adult slices and in the basal versus apical dendritic fields. There were no evident age-related or regional differences in the concentrations of A1 receptors (Rex et al., 2005) and the affinity of rat

brain A1 receptors is reported not to change with age (Cunha et al., 1995; Sperlagh et al., 1997). Extracellular adenosine levels are elevated in brains (Murillo-Rodriguez et al., 2004) and hippocampal slices (Sperlagh et al., 1997) from aged (22–24 months) rats with a trend in the same direction in slices from 12-month-old rats. Moreover, adenosine removal appears to be slower in slices prepared from aged rats than in those from young adults (Cunha et al., 2001). These observations, together with the slower washout effect in middle-aged slices, point to failures in extracellular clearance, rather than enhanced signaling, as the explanation for the failure of LTP in the middle aged str. oriens.

Disturbances involving extracellular adenosine have been implicated in age-related sleep disorders (Murillo-Rodriguez et al., 2004). The results just described extend this line of work by suggesting that problems with levels of adenosine clearance begin relatively early in adult life, at which time they have a significant impact on synaptic plasticity. Moreover, results from our LTP studies indicate that age-dependent changes in adenosine processing are more pronounced in some regions than others, an observation that should be of help in the search for the cellular bases of the changes.

As noted, age-dependent decreases in positive modulators of LTP could also contribute to deficits in potentiation and memory function with age. This raises the questions of whether levels of the one known positive LTP modulator, BDNF, decline with age, and, in particular, are reduced in middle-aged animals. Although hippocampal BDNF gene expression is consistently found to be decreased in Alzheimer's disease (Phillips et al., 1991; Murray et al., 1994; Connor et al., 1997), reports of age effects on BDNF expression in rodents have been mixed. Hattiangady and colleagues (2005) found hippocampal BDNF immunoreactivity was significantly reduced from young adulthood to middle age (4 versus 12 months) with no further change afterwards in male Fischer 344 rats. In contrast, other groups report hippocampal BDNF protein levels are significantly increased from 2 to 6 months of age (and stable from 6 to 18 months) in Fischer 344 rats (Narisawa-Saito and Nawa, 1996) and modestly but significantly increased from 10 to 18–29 months of age in Fischer 344 X Brown Norway rats (Newton et al., 2005). In similar age comparisons, Adlard et al. (2005) did not detect significant age-related changes in BDNF protein content in mouse hippocampus. It is possible that differences in ELISA antisera and rodent strains contributed to the sharp differences in results across these studies, but at this point no clear story has emerged as to whether BDNF levels decrease with normal aging. Future studies will need to include specific assays for mature BDNF proteins. Recent work suggests that BDNF is released in 'pro-forms' (estimated at 19–34 kD) that are cleaved to generate mature, 13–14 kD BDNF. Both pro- and mature BDNF proteins can mediate neurotrophin signaling but the mature form is argued to be the variant that supports LTP and neuronal viability (Pang et al., 2004; Lu et al., 2005; Woo et al., 2005). Because ELISA studies so far reported used antisera that detect both pro- and mature BDNF proteins, it is possible that age-related changes in the latter, LTP-related form of the neurotrophin, were obscured by relatively stable levels of its larger precursor.

7. Therapeutic strategies for treating age-related plasticity deficits

The above analysis of LTP as a redundant system with modulators provides a framework with which to consider possible therapeutics. The evidence that age-related deficits in LTP

arise from overactivity of a normally present negative modulator suggests that an antagonist of that modulator might be appropriate, an idea made all the more attractive by the observation that such a compound restored LTP in middle-aged slices. However, antagonists of the adenosine A1 receptor are psychomotor stimulants and have broad effects outside the glutamatergic system (Fisone et al., 2004); nonetheless, it would be interesting to determine if concentrations that restore LTP are below the range where unacceptable side-effects would appear. The straightforward strategy of accelerating adenosine clearance lacks the necessary pharmaceuticals and, in any event, seems unlikely to succeed because of the important actions of the purine throughout the body. Further ideas along this line could arise if the causes of the adenosine disturbance were to be identified.

7.1. Induction and consolidation

An indirect approach for enhancing deficient potentiation, as opposed to directly addressing the origins of the adenosine-based problem, has some reasonable chance of success because, as emphasized in the redundancy model, there are many potential targets to choose from. Current efforts appear to be focused on induction and consolidation. The introduction of drugs ('ampakines') that positively modulate AMPA receptors in brain (Staubli et al., 1994a,b) is of interest because ampakines increase and prolong the EPSPs needed to unblock NMDA receptors, and thereby facilitate LTP induction (Staubli et al., 1994b). Moreover, acute administration of ampakines restores LTP to the basal dendrites of middle-aged slices (Rex et al., 2005) and improves memory scores in middle age rats (Granger et al., 1996) as well as elderly humans (Lynch et al., 1997).

Given these encouraging observations, the potential for using ampakines as therapeutics comes down to side effects. In this regard it is important to note that the drugs fall into two broad categories: variants that increase (i) the amplitude or (ii) both the amplitude and duration of the synaptic response. Members of the former, less potent group have been tested extensively in preclinical and clinical safety trials without significant side effects (Lynch, 2006). Whether the drugs produce significantly large gains in excitatory transmission to offset the age-related impairment to LTP remains to be determined; if so, then these 'amplitude' drugs constitute reasonable candidates for therapeutic use. The 'amplitude/duration' compounds reverse the LTP and memory deficits associated with middle age but are not as safe as the amplitude drugs, and in particular are more prone to cause seizures. It is likely, though, that these compounds will have more potent effects on age-related losses of plasticity.

Efforts to promote consolidation have largely dealt with the late, protein synthesis-dependent period (rather than the cytoskeletal assembly phase) and, in particular, on the cAMP responsive element binding protein (CREB) family of transcription factors (Lynch, 2002; Josselyn and Nguyen, 2005). CREB, after having been phosphorylated (and activated) binds to the cyclic AMP response element of target genes. The factor plays an essential role in *Aplysia* long-term facilitation (Dash et al., 1990) and is reported to be important for the maintenance of LTP (Barco et al., 2002). As expected from these physiological results, several studies have documented a role for CREB in long-term memory in *Drosophila* and mice (Josselyn and Nguyen, 2005). These results suggest that increasing CREB activity would both facilitate LTP and the memory arising from it. One approach to achieving this

would be to slow the hydrolysis of cAMP (which drives the kinase that activates CREB) by inhibiting the phosphodiesterase isozyme PDE-IV. This is reported, under some conditions at least, to increase CREB phosphorylation and CREB binding to DNA as well as retention scores in rats (Nagakura et al., 2002). Whether similar treatments would offset age-related failures of LTP is not known but, in any event, side effects associated with currently available PDE IV inhibitors are probably unacceptable (Zhu et al., 2001). Given the ubiquitous distribution of CREB, target selectivity (brain/forebrain) will be a critical requirement for drugs acting upon it to produce cognitive effects.

7.2. Modulators

An alternative approach to enhancing LTP, and potentially memory, would be to increase the potency of positive modulators. It appears that this strategy may be associated with fewer major side-effects than those discussed above. In particular, recent studies indicate that levels of brain BDNF are malleable and increases can be sustained long enough to be therapeutically useful.

A variety of manipulations increase BDNF production in brain but most of these (e.g., seizures, chronic treatment with antidepressants or cannabinoids) (Isackson et al., 1991; Castren, 2003; Butovsky et al., 2005; Torregrossa et al., 2005) would not be suitable for treating age-related losses of synaptic plasticity. BDNF levels are also higher in rats and mice with elevated levels of voluntary exercise (wheel running) relative to non-running, age-matched controls (Cotman and Berchtold, 2002; Farmer et al., 2004) but it is not clear that this provides a route for increasing the neurotrophin in subjects living in normal environments where locomotor activity is commonplace. Moreover, in an analysis of exercise effects in mice of different ages, Adlard et al. (2005) found that elevated BDNF protein levels were sustained for weeks in young adults but were transient in middle-aged and old mice.

The BDNF gene is up-regulated by excitatory input (Gall and Lauterborn, 2000), from which it follows that ampakines should increase production of the neurotrophin. This prediction has been confirmed for cultured neurons (Legutko et al., 2001), organotypic slices (Lauterborn et al., 2001), and the brain in vivo (Lauterborn et al., 2001). In the cultured slice studies, 10-fold increases in BDNF protein were obtained with the 'amplitude/duration' drugs (Lauterborn et al., 2001); the 'amplitude only' compounds appear to be significantly less effective. Increases of lesser magnitude were also obtained in vivo, and at ampakine doses that produced no evident disturbances to behavior.

An intriguing feature of the induced increases in BDNF is that they require only relatively brief exposures to the ampakines; i.e., large effects on BDNF protein can be sustained with intermittent drug treatments (Lauterborn et al., 2003) and recent work indicates that pulse treatments as short as 3 h can effectively increase neuronal BDNF levels for days (unpublished data). This most probably occurs because BDNF gene expression is induced with very brief increases in neuronal activity (seconds) (Castren et al., 1998) after which mRNA levels remain elevated for hours and elevated BDNF protein levels persist for days (Gall and Lauterborn, 2000). Combining these features results in a system in which a transient increase in EPSPs can quickly increase BDNF mRNA levels for hours and BDNF protein content for days. Recent work based on these

observations indicates that in vivo treatments (i.p. injections) with short-lived ampakines (half-life < 30 min) cause significant, long-lasting increases in cortical and hippocampal BDNF protein levels in both young adult (2–3 months) and in middle-aged (8–10 months) rats. In middle-aged animals, this is associated with a restoration of LTP in the CA1 basal dendrites as assessed in tests carried out many hours after the drug injection (Rex et al., 2006).

The above results suggest a novel pharmacological strategy for reversing age-related losses in plasticity, one in which brief drug treatments are used to produce prolonged periods of restored function. This would reduce the impact of any side-effects associated with the ampakine. However, there is little information regarding unwanted effects that might accrue with extended periods of high BDNF levels.

8. Relationship of plasticity deficits to generalized brain aging

Attempts to understand the origins of age-related losses in synaptic plasticity inevitably come to the question of whether such effects occur in isolation or instead are secondary to some more basic form of brain aging. In the present instance, the issue reduces to whether the adenosine change is one of a set of early appearing aging effects as opposed to being tied to a fundamental shift that emerges shortly after maturation ends. Surprisingly little has been written about brain changes in the period of life under discussion, and there is certainly nothing like an agreed upon basic modification that drives numerous other, slower-to-develop manifestations of aging. This is not to say that early developing, progressive features related to aging are unknown. The best known example is the accumulation of lipofuscin, a complex mixture of peroxidized lipids, proteins, and transition metals resulting from the incomplete breakdown of phagocytosed material by the endosome/lysosome system (Kitani et al., 1995). Lipofuscin begins to appear early in adult life (age 2 months in rat hippocampus) and then accumulates steadily thereafter (Oenzil et al., 1994; Bi et al., 2001b; Lynch and Bi, 2003). Although an unlikely stimulus for age-related changes in brains, its presence indicates that lysosomal dysfunction begins very early in adulthood and worsens with time (Fig. 5).

There are also multiple reasons for assuming that changes to the endosome/lysosome system initiate characteristic features of the aging brain (see Fig. 6). Partial suppression of lysosomal proteases causes a rapid and dramatic increase in the number of neuronal lysosomes and concentrations of ceroid-lipofuscin in the brains of young adult rats (Ivy et al., 1984). Cultured hippocampal slice experiments have shown that inhibitors selective for cathepsins B and L generate large swellings of the axon as it emerges from the soma (meganeurites) (Bednarski et al., 1997; Bi et al., 1999), a characteristic feature of pyramidal cells in the aged human cortical telencephalon (Braak, 1979). Comparable experiments using slices from apolipoprotein E knock-out mice produced evidence of intraneuronal neurofibrillary tangles (Bi et al., 2001b) which, like meganeurites, occurred in regions where they are prominent in humans (Bi et al., 1999; Yong et al., 1999). There are at least three pathways over which dysfunction produces these and other features of brain aging. *First*, conditions that interfere with normal operation cause lysosomes to proliferate, something that in some neurons leads to large accumulations of fused, dense

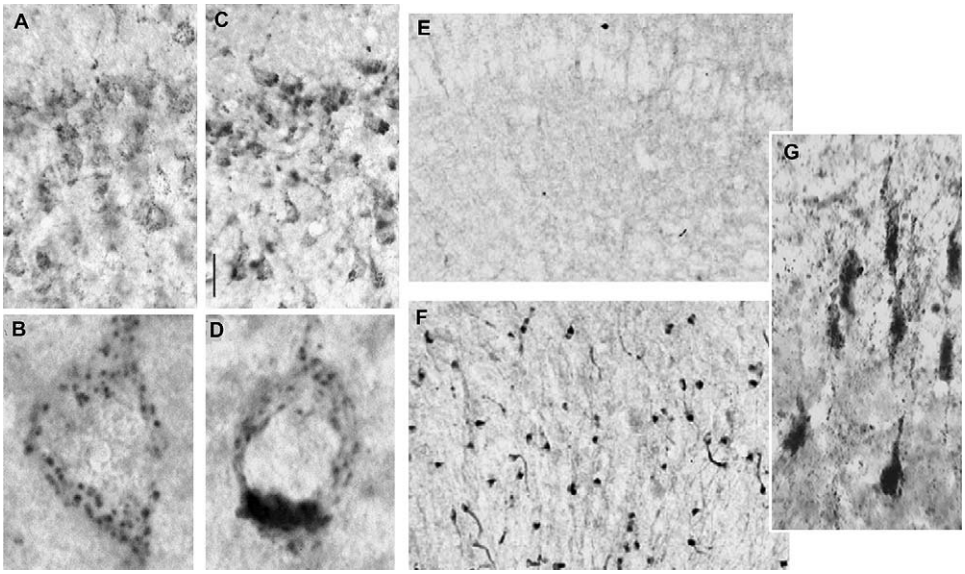

Fig. 5. Lysosomal abnormalities in early middle age and their potential consequences. (A–D) Comparison of lysosomal (cathepsin D) immunostaining in layers II/III of the entorhinal cortex in young adult and middle-aged rats. Panel (A) is a survey micrograph and panel (B) a higher power image of the cortex in a 2-month-old rat. Panels (C) and (D) are equivalent images from a 12-month-old animal. Note the polar accumulation of lysosomes in the older rat (B vs. D). (E, F) Immunostaining for hyperphosphorylated tau protein in cultured hippocampal slices prior to (E) and 6 days after (F) blocking two lysosomal proteases. (G) Conventional silver staining for neurofibrillary tangles in a slice in which two lysosomal proteases had been inhibited for 6 days.

secondary bodies in the periphery of the cell body. This process appears to be responsible for the formation of meganeurites (Bednarski et al., 1997) and similar structures found in primary dendrites (‘dendritic spikes’, Bi et al., 2003). These pathological features likely disrupt transport between the cell body and its processes by displacing and distorting the tubule system. *Second*, lysosomal dysfunction is accompanied by the leakage of proteases into the cytoplasm (Fig. 6). Cathepsin D is of particular interest because of work showing that it retains activity at neutral pH and continues functioning after having left the acidic environment of the lysosomal interior (Bednarski and Lynch, 1996). The extralysosomal presence of these hydrolases will cause aberrant proteolysis and thus disruption of multiple cell systems. The breakdown products resulting from the proteolysis may also be atypical and pathogenic; there is evidence that cytoplasmic cathepsin D produces a tau protein fragment comparable to that thought to ‘seed’ the formation of neurofibrillary tangles (Bednarski and Lynch, 1996, 1998), while inhibitors of the enzyme block the development of phosphorylated tau deposits (Bi et al., 2000). *Third*, metabolism within lysosomes generates products necessary for proper functioning of the endoplasmic reticulum, the loss of which can impair calcium buffering (Jmoudiak and Futerman, 2005). This would have a diverse array of effects including activation of the calcium-sensitive protease calpain (Fig. 6), an enzyme linked to a diverse array of pathologies. Calpain, like cathepsin D, is thought to produce aberrant fragments that assemble, or trigger the assembly of, aberrant

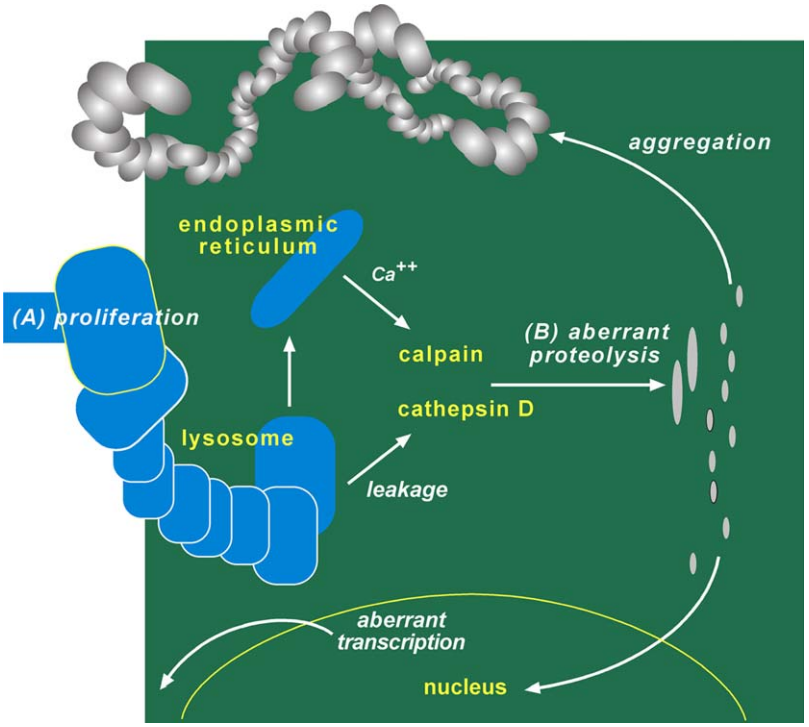

Fig. 6. Hypothesis that lysosomal dysfunction is an important contributor to normal brain aging. (A) Interference with lysosomal proteases causes a rapid multiplication of lysosome-like bodies; these accumulate and eventually choke off transport between the neuronal cell body and its processes. (B) Dysfunction results in the leakage of lysosomal proteases into the cytoplasm where they create abnormal breakdown products. These fragments in turn 'seed' the formation of aberrant intracellular structures that characterize the aged brain (e.g., tangles) and enter the nucleus where they affect transcription. Dysfunction also interferes with the metabolic products lysosomes provide other organelles including the endoplasmic reticulum (ER). These disturbances interrupt the normal calcium buffering function of the ER, leading to activation of calcium sensitive enzymes including calpain, a protease that generates aberrant breakdown products.

intracellular structures such as the inclusions that characterize Huntington's Disease (Sun et al., 2002). The huntingtin protein fragments accumulate in the nucleus where they may gain access to the cell's transcription apparatus.

In all, we suggest that changes in the endosome/lysosome system, acting through multiple routes, constitute a plausible candidate for a generator of aging during early adulthood. Could they disrupt plasticity, perhaps by interfering with the cell machinery that regulates extracellular adenosine? The accumulation effect that follows lysosomal dysfunction occurs in a polarized fashion with the greatest concentrations of primary and secondary bodies found in zones of the cell bodies where apical or basal dendrites emerge (Fig. 5) (Lynch and Bi, 2003). Such effects are suggestive of transport problems that could differentially affect apical versus basal dendritic domains. But other than this, there are no obvious links between the broad phenomena created by lysosomal dysfunction and the apparently more selective alterations that impair LTP. This, we can suspect, will be a

general problem for attempts to explain discrete failures in terms of global hypotheses about brain aging: how do fundamental changes in (for example) cell organelles affect so few endpoints, at least in the early stages of adulthood? A sensible place to begin addressing this question would be to design experiments to test the proposed linkage. In the present case, we could ask if experimentally induced lysosomal dysfunction affects adenosine clearance and LTP in advance of other physiological measurements. And the evidence that lysosomal abnormalities, as seen in immunocytochemical mapping, are not homogenously distributed during early middle age makes possible testing for regional correlations between lysosomal pathology and age-related losses in plasticity. Experiments along these lines would challenge the hypothesis and, if successful, point to ways for identifying intermediates between the proposed aging mechanism and the observed functional endpoint.

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