Aging Differentially Alters Forms of Long-Term Potentiation in Rat Hippocampal Area CA1

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Shankar, Subbakrishna, Timothy J. Teyler, and Norman Robbins. Aging differentially alters forms of long-term potentiation in rat hippocampal area CA1. *J. Neurophysiol.* 79: 334–341, 1998. Long-term potentiation (LTP) of the Schaffer collateral/commissural inputs to CA1 in the hippocampus was shown to consist of *N*-methyl-D-aspartate receptor (NMDAR) and voltage-dependent calcium channel (VDCC) dependent forms. In this study, the relative contributions of these two forms of LTP in in vitro hippocampal slices from young (2 mo) and old (24 mo) Fischer 344 rats were examined. Excitatory postsynaptic potentials (EPSP) were recorded extracellularly from stratum radiatum before and after a tetanic stimulus consisting of four 200-Hz, 0.5-s trains given 5 s apart. Under control conditions, a compound LTP consisting of both forms was induced and was similar, in both time course and magnitude, in young and old animals. NMDAR-dependent LTP (nmdaLTP), isolated by the application of 10 μM nifedipine (a voltage-dependent calcium channel blocker), was significantly reduced in magnitude in aged animals. The VDCC dependent form (vdccLTP), isolated by the application of 50 μM D,L-2-amino-5-phosphonvalerate (APV), was significantly larger in aged animals. Although both LTP forms reached stable values 40–60 min posttetanus in young animals, in aged animals vdccLTP increased and nmdaLTP decreased during this time. In both young and old animals, the sum of the two isolated LTP forms approximated the magnitude of the compound LTP, and application of APV and nifedipine or genestein (a tyrosine kinase inhibitor) together blocked potentiation. These results suggest that aging causes a shift in synaptic plasticity from NMDAR-dependent mechanisms to VDCC-dependent mechanisms. The data are consistent with previous findings of increased L-type calcium current and decreased NMDAR number in aged CA1 cells and may help explain age-related deficits in learning and memory.

INTRODUCTION

Aged animals do not learn as well as young animals, particularly in tasks that require spatial memory. Several lines of evidence have implicated the hippocampus as a possible locus for this deficit. Lesions of the hippocampus impair spatial memory in young rats (Buzsaki et al. 1980; Morris et al. 1982; Olton et al. 1978b; Sutherland et al. 1983) and their performance on behavioral tests becomes similar to aged rats (Winocur and Moscovitch 1990; Winocur 1992). The hippocampus is hypothesized to represent a spatial map, as cell firing is correlated with the animal's position in its environment (Hill 1978; McNaughton et al. 1983; Olton et al. 1978a). In addition, neurons in the hippocampus exhibit long term potentiation (LTP), a long-lasting, use-dependent modification of synaptic strength, which may be a cellular substrate of learning and memory (Bliss and Collingridge 1993; McNaughton and Morris 1987; Teyler and DiScenna 1984). Alterations in hippocampal LTP may therefore be involved in age-related learning deficits.

LTP was extensively studied in hippocampal slice preparations. In young animals, a 100-Hz tetanus applied to the Schaffer collateral/commissural inputs to CA1 cells reliably induces an LTP that lasts for hours (Bliss and Collingridge 1993). This potentiation is prevented by the blockade of postsynaptic *N*-methyl-D-aspartate receptors (NMDAR) by D,L-2-amino-5-phosphonvalerate (APV), suggesting that it is an NMDAR-dependent alteration in synaptic strength (termed nmdaLTP). When NMDARs are completely blocked by APV, a stronger tetanus (200 Hz) also induces a long-lasting, APV *insensitive* potentiation, which can be prevented by the application of nifedipine, a blocker of L-type Ca^{2+} channels (Cavus and Teyler 1996; Grover and Teyler 1990, 1992, 1994). The stronger tetanus may be required for the induction of this voltage dependent calcium channel (VDCC) dependent form of LTP (termed vdccLTP) because the activation of L-type Ca^{2+} channels requires a large postsynaptic depolarization (Grover and Teyler 1992). The two forms of LTP appear to activate different signal transduction pathways as inhibiting serine-threonine kinases selectively blocks nmdaLTP, whereas inhibitors of tyrosine kinases block vdccLTP (Cavus and Teyler 1996). In the absence of APV, a 200-Hz tetanus induces a compound potentiation, consisting of two pharmacologically separable components: nmdaLTP and vdccLTP.

Previous studies of the effects of aging on CA1 hippocampal LTP indicated either no change or a reduced LTP in aged animals. Most studies used relatively strong tetanus parameters and found no difference between young and old animals (Barnes et al. 1996; Chang et al. 1991; Deupree et al. 1993; Landfield et al. 1978; Moore et al. 1993). These strong tetani may have activated both nmdaLTP and vdccLTP, producing a compound LTP. In experiments that used a weaker tetanus (Moore et al. 1993), aged animals show reduced LTP magnitude and duration. The weaker ''primed burst'' tetanus used by Moore et al. (1993) may not have depolarized the postsynaptic cells sufficient to activate VDCC's, so the LTP induced may be exclusively nmdaLTP. If so, these results suggest a decline in NMDAR number or function in aged rats. As the compound LTP is similar in the two age groups, the decreased nmdaLTP in aged animals implies an increased vdccLTP. For example, such an increase might be the result of a greater Ca^{2+} current through L-type channels in aged animals.

There is evidence for both an NMDAR deficit and an increase in L-type Ca^{2+} current in aged animals. The number

of NMDA receptors was found to decrease in aged rat hippocampus (Clark et al. 1992; Magnusson and Cotman 1993a, 1993b; Tamaru et al. 1991; Wenk et al. 1991). Moreover the performance of aged rats on a spatial memory test is correlated with the number of NMDA receptors in their hippocampi (Davis et al. 1993) and their performance is improved by the infusion of an NMDAR agonist. Several lines of evidence suggest that CA1 cells in aged animals have a larger L-type Ca^{2+} current. These cells have a prolonged afterhyperpolarization after a burst (Landfield and Pitler 1984; Kerr et al. 1989; Moyer et al. 1992), indicating a greater activation of Ca^{2+} activated K^+ current, which is reduced by blocking L-type Ca^{2+} channels with nimodipine (Moyer et al. 1992). Calcium action potentials are longer in aged animals (Moyer and Disterhoft 1994; Pitler and Landfield 1990) and are similarly reduced by nimodipine (Moyer and Disterhoft 1994). Recent direct measurements of L-type Ca^{2+} current have shown a three- to fourfold increase in aged CA1 cells (Campbell et al. 1996; Thibault and Landfield 1996). Chronic nimodipine administration to old animals was shown to facilitate learning, suggesting that excessive Ca^{2+} influx through L-type channels interferes with learning in these animals (Kowalska and Disterhoft 1994; Schuurman et al. 1987; Thompson et al. 1990).

We hypothesized that both nmdaLTP and vdccLTP are present in the CA1 region of aged animals and that, given appropriate activation, both could be expressed. Pharmacological dissection of the two forms of LTP might reveal aging induced alterations in their properties, such as time course, magnitude, stability, and activation of kinase cascades. We report here experiments on in vitro hippocampal slices from young (2 mo) and old (24 mo) Fischer 344 rats in which we examined these two forms of LTP after a 200-Hz tetanus.

METHODS

Animals

Young (6–9 wk) and old (24 mo) male, virgin Fischer 344 rats were obtained from the NIA colony at Harlan Laboratories. At least three days were allowed for rats to equilibrate before experimentation. Rats were housed in microisolator cages and given food and water ad libitum.

Slice preparation and maintenance

Rats were decapitated without anesthesia. After rapid hippocampal dissection, 400 μm thick slices were cut cold in a vibrating slicer and placed into an interface recording chamber or a room temperature holding chamber. In the interface recording chamber slices sat on a nylon mesh perfused with 0.7 ml/min artificial cerebrospinal fluid (ACSF) composed of (in mM) 125.0 NaCl, 3.35 KCl, 1.25 NaH_2PO_4, 2.0 $MgSO_4$, 2.0 $CaCl_2$, 25.0 $NaHCO_3$, and 10.0 D-glucose, equilibrated with 95% O_2-5% CO_2. The chamber was brought from room temperature to 32–33°C over 30 min and recordings were started 30 min later. Slices from the holding chamber that were later moved to the recording chamber were allowed to equilibrate for at least 30 min.

Electrophysiology

Schaffer collateral/commissural axons in the CA1 region were stimulated by a concentric bipolar microstimulating electrode applying monophasic, 100 μs duration voltage pulses. Recordings were made through a glass microelectrode filled with 2.0 M NaCl (4–6 MΩ). Signals were amplified by a factor of 1,000, bandpass filtered at 1 Hz to 5 kHz, digitized at 10 kHz with a 12-bit resolution, and stored in a computer for later analysis with the Labman program (Borroni et al. 1991). The recording electrode was first placed in the CA1 cell body layer and evoked responses were recorded every 30 s as the stimulus voltage was slowly increased. Once the population spike threshold was found, the recording electrode was moved to the corresponding dendritic layer and the amplitude of the evoked field excitatory postsynaptic potential (fEPSP) was measured. The stimulus voltage was then decreased until the fEPSP was one-half of this amplitude. This voltage was used for the test pulses and the voltage at population spike threshold was used for tetanic stimulation. This procedure normalized the stimulation intensity across slices and provided a large dynamic range for synaptic strength changes. The presynaptic fiber volley was monitored as an index of response stability. We observed no changes in the fiber volley after drug application.

The baseline synaptic strength was determined by test pulses given every 30 s. Slices in which the baseline was not stable for at least 20 min or whose fEPSP amplitude was <0.5 mV were rejected. Stable slices were tetanized by giving four 200-Hz, 0.5-s trains, 5 s apart. Test pulses every 30 s continued for at least 60 min after the tetanus.

Drug application

A stock solution of each drug was made up, aliquotted, and frozen at −20°C. Aliquots were thawed only once and final solutions were added to the ACSF perfusion line 20 min before the tetanus was applied. Drugs used were D,L-APV (50 μM), nifedipine [10 μM with 0.01% dimethyl sulfoxide (DMSO), used in a darkened room], genistein, and daidzein (20 μm, 0.02% DMSO), all purchased from Research Biochemicals Incorporated. Drug perfusion did not affect the baseline fEPSP slope or amplitude.

Data analysis and statistics

The peak slope of the initial 0.5 ms downward phase of the fEPSP was measured and used as an index of synaptic strength. For each slice, the fEPSP slopes were normalized against the average slope over the 5 min before the tetanus. To determine whether or not a slice was significantly potentiated ($P < 0.05$), the individual fEPSP slopes during the last 20 min of baseline were compared with the fEPSP slopes from 40 to 50 min after the tetanus by using a two-tailed Student's *t*-test.

For group comparisons, slices from the same animal that received the same treatment were averaged together and represented an *n* of one. This procedure prevented the results from being greatly skewed by one animal (Barnes 1994). The mean magnitudes of potentiation of two groups were compared by using a two tailed *t*-test. To examine the time course of potentiation within each group the normalized fEPSP slopes for each time point were averaged and a linear regression line was fit over the time 40–60 min after the tetanus. The potentiation within a group was judged to be stable if the regression slope was not significantly different from zero ($P < 0.05$) by a two-tailed *t*-test. Regression slopes between groups were also compared by a two-tailed *t*-test.

RESULTS

Baseline physiology

The baseline-evoked response in slices from both young and old animals consisted mainly of a large negative fEPSP, which was in some slices preceded by a presynaptic fiber volley (Fig. 1). Multiple spiking was reported to occur more frequently in aged hippocampus (Bauman et al. 1992), but

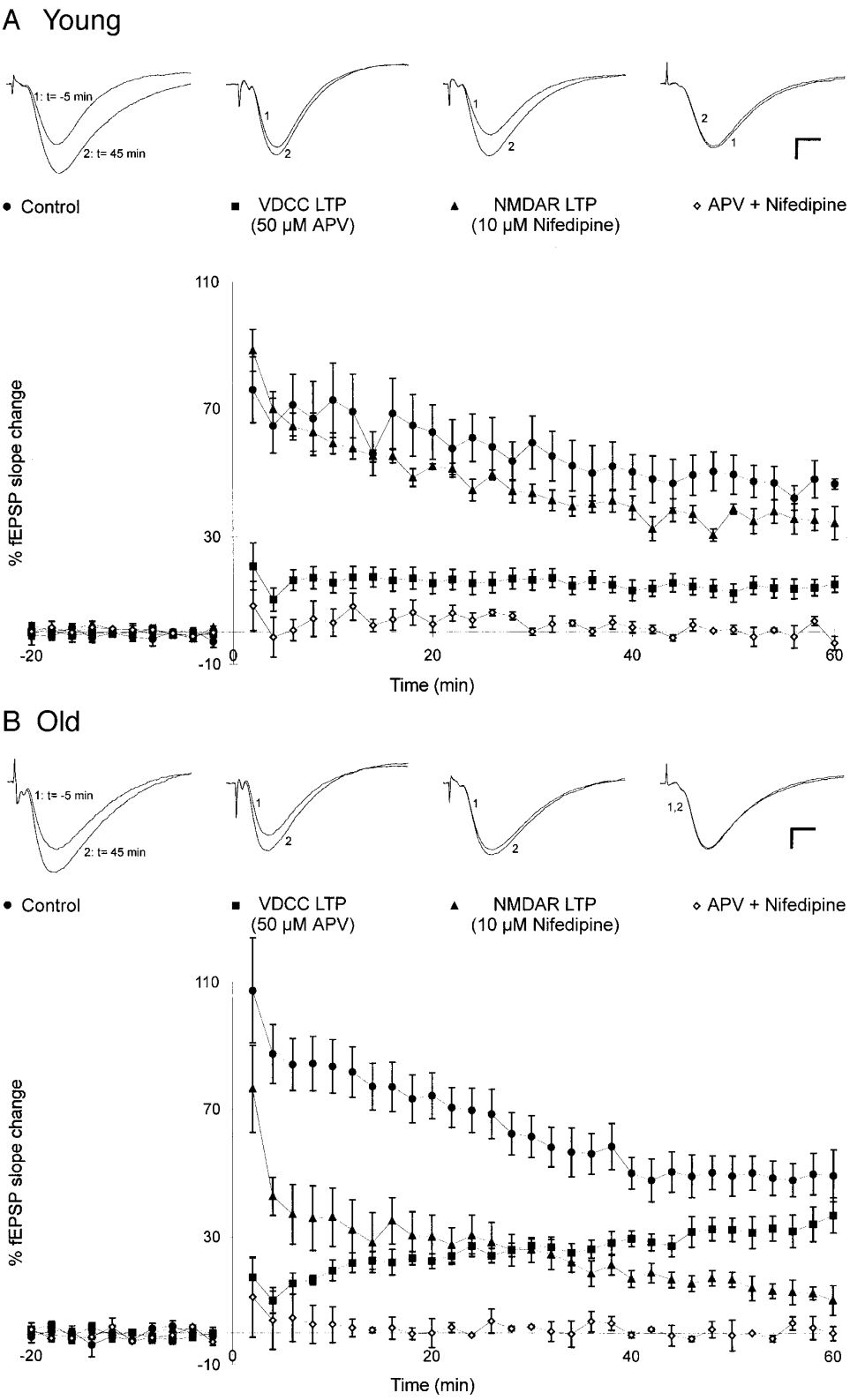


FIG. 1. Long-term Potentiation (LTP) in young (*A*) and old (*B*) slices after a 200-Hz tetanus given at time 0. Mean ± SE of percentage change from baseline fEPSP slope for each group is shown every two min. Control animals (●) of both ages ($n = 6$ young, 6 old) displayed a large compound potentiation [sum of voltage-dependent calcium channel LTP (vdccLTP) and *N*-methyl-D-aspartate–dependent LTP (nmdaLTP)] that decayed to a stable LTP by 40–60 min. VdccLTP (■) was induced by tetanizing in presence of 50 μM D,L-2-amino-5-phosphonvalerate (APV) and resulted in a small and stable potentiation from young animals ($n = 8$) and larger and increasing potentiation from old animals ($n = 6$) that was of significantly greater magnitude at 40–50 min ($P < 0.01$). NmdaLTP (▲) was induced by tetanizing in presence of 10 μM nifedipine and resulted in a large potentiation that decayed to a stable value from young animals ($n = 5$) and a smaller initial potentiation that nearly decayed to baseline in old animals ($n = 5$) and was of significantly smaller magnitude at 40–50 min ($P < 0.01$). Animals tetanized in presence of both APV and nifedipine (◇) failed to potentiate. *Insets*: representative evoked field excitatory postsynaptic potentials (fEPSPs) from one slice in each group taken 5 min before (1) and 45 min after (2) tetanus. Scale bar: 0.5 mV, 5 ms.

was not seen in slices from either young or old animals. There were no consistent age variations in the stimulus intensity used for test pulses and tetani, nor in baseline f EPSP slopes (tetanus pulse strength: young, 11.0 ± 1.17 (SE) V; old, 12.4 ± 1.29 V; $P > 0.4$) (baseline f EPSP slope: young, $-1.02 \pm 0.094\ \mathrm{V \cdot s^{-1}}$; old, $-0.88 \pm 0.087\ \mathrm{V \cdot s^{-1}}$; $P > 0.2$).

Control LTP

Slices from six young and six old animals received the 200-Hz tetanus in control ACSF. The responses were similar for both age groups. Both showed an initially large potentiation that decayed to a stable LTP (Fig. 1, regression slope

over 40–60 min posttetanus not significantly different from zero; Fig. 1*A*, young, $P > 0.8$; Fig. 1*B*, old, $P > 0.12$) that was not significantly different between the two age groups (Fig. 2; $P > 0.6$).

Effect of age on forms of LTP

VdccLTP was induced by applying a 200-Hz tetanus to slices from eight young and six old rats in the presence of 50 μM APV. In both groups LTP developed (Fig. 1, *A* and *B*). In young animals (Fig. 1*A*) the LTP was stable (regression slope not significantly different from zero; $P > 0.7$), but in the old group (Fig. 1*B*) the potentiation continued to increase significantly over the time 40–60 min posttetanus (0.34 ± 0.024%/min; $P < 0.01$). When averaged over the 40–50 min posttetanus, vdccLTP was significantly greater in old than in young animals (Fig. 2; $P < 0.01$).

In contrast, a 200-Hz tetanus applied in the presence of 10 μM nifedipine to induce nmdaLTP produced an initially large potentiation that decayed slowly (Fig. 1, *A* and *B*). The response in the young animals (Fig. 1*A*) reached a stable value ($n = 5$; regression slope not significantly different from zero; $P > 0.9$), but in the old animals (Fig. 1*B*) the synaptic strength continued to decrease over 40–60 min posttetanus ($n = 5$; regression slope -0.52 ± 0.054%/min; $P < 0.01$). The magnitude of the potentiation over 40–50 min posttetanus was significantly smaller in old than in young animals (Fig. 2; $P < 0.01$).

To determine whether or not any lasting potentiation could be induced that was independent of both forms of LTP, three slices each from young and old animals were tetanized in the presence of both 50 μM APV and 10 μM nifedipine. No lasting potentiation was observed in either age group (Figs. 1, *A* and *B*, and 2). For all of the slices the fEPSP slopes 40–50 min posttetanus were not significantly different from their baselines ($P > 0.2$ for all slices).

Tyrosine kinase inhibition

Although these results indicate an aging induced alteration in the proportions of nmdaLTP and vdccLTP, it was not clear whether or not this effect is the result of changes in Ca^{2+} entry or in the biochemical cascades that occur after Ca^{2+} entry. VdccLTP was found to require in young animals the activation of a tyrosine kinase cascade (Cavus and Teyler 1996). To control for the possibility that the larger proportion of vdccLTP in aged rats might result from the activation of other kinase pathways, we examined both forms of LTP in young and old rats after blockade of tyrosine kinases with the specific tyrosine kinase inhibitor genistein (Akiyama et al. 1987; O'Dell et al. 1991). If the proportionally greater vdccLTP seen in old rats results from activation of tyrosine kinase cascades, we would expect genistein to be more effective in blocking compound LTP in old rats than young rats.

Tetanic stimulation in normal ACSF with 20 μM genistein resulted in a significantly smaller potentiation than in control solution in both young (Fig. 3*A*, $n = 6$; $P < 0.05$) and old (Fig. 3*B*, $n = 5$; $P < 0.015$) animals. Genistein had a differential effect on young and old animals. In young animals, the potentiation after genistein application was stable over the time 40–60 min posttetanus (regression slope 0.0186 ± 0.065%/min; not significantly different from 0; $P > 0.75$), whereas in old animals there was a declining potentiation over this time (regression slope -0.41 ± 0.055%/min; significantly different from zero; $P < 0.01$). The magnitude of the potentiation averaged over 40–50 min posttetanus was significantly smaller in aged rats ($P < 0.02$). Thus the tyrosine kinase inhibitor genistein had a more pronounced compound LTP blocking effect in slices from old rats, which express relatively more vdccLTP than nmdaLTP.

At both ages, the responses in the presence of the tyrosine kinase inhibitor genistein were similar to the respective responses in the presence of the VDCC blocker nifedipine. The magnitude of the potentiation averaged over 40–50 min posttetanus was not significantly different between genistein and nifedipine in young (Fig. 1*A* vs. 3*A*, $P > 0.073$) and old (Fig. 1*B* vs. 3*B*, $P > 0.61$) rats. Both drugs blocked LTP to a greater extent in old than in young rats.

To determine if nifedipine was blocking the Ca^{2+} channels contributing to the signal transduction cascade affected by

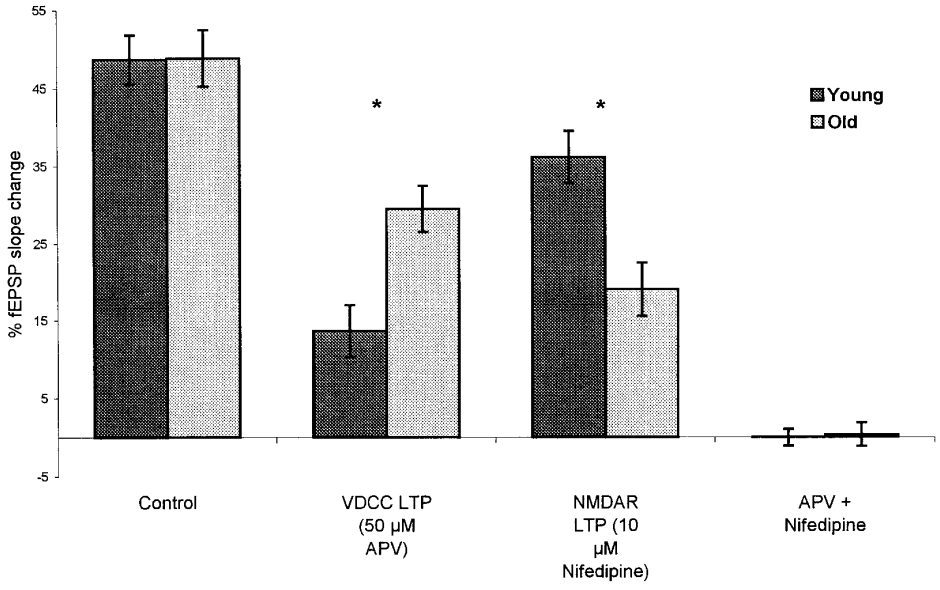
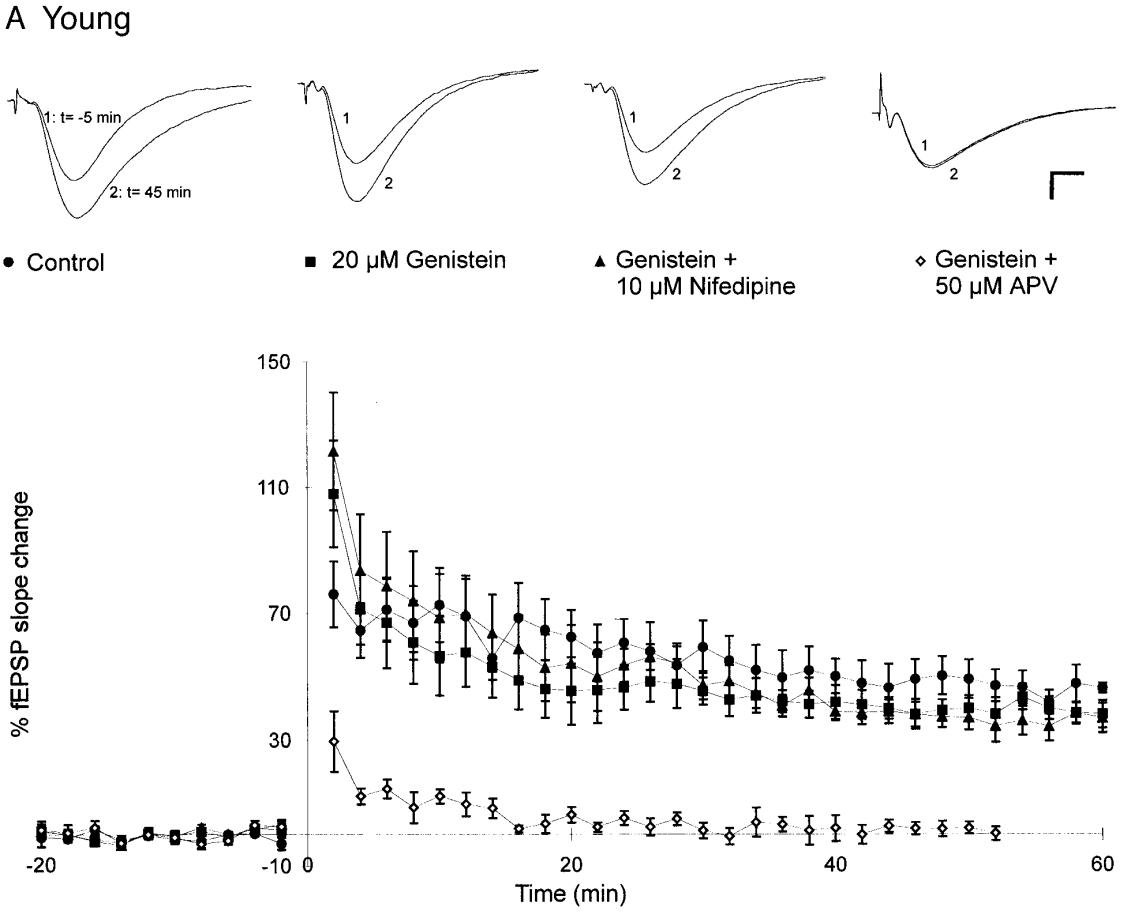


FIG. 2. Group mean ± SE potentiation magnitude of data of Fig. 1 measured 40–50 min after a 200-Hz tetanus in slices from young and old animals under indicated conditions. * Statistically significant ($P < 0.01$) differences between young and old animals. Data show that vdccLTP is prominent in old animals whereas nmdaLTP is predominant in young animals. Control animals, exhibiting a compound LTP consisting of sum of both forms, do not differ across age, suggesting existence of compensatory processes that maintain constant overall level of synaptic plasticity across age.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Time (min)
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genistein, 20 μM genistein and 10 μM nifedipine were applied together (young, $n = 5$; old, $n = 5$; Fig. 3). At both ages, this combination produced a potentiation that was not significantly different from genistein alone in magnitude (young, $P > 0.68$; old, $P > 0.50$). In young animals, the potentiation was stable (regression slope 0.047 ± 0.053%/min; not significantly different from 0; $P > 0.38$), whereas in old rats the potentiation declined significantly (regression slope −0.369 ± 0.052%/min; $P < 0.01$).

To confirm that blockade of NMDARs and tyrosine kinases together prevents potentiation, slices from young ($n = 3$) and old ($n = 3$) rats were stimulated in the presence of 20 μM genistein and 50 μM APV. In both age groups no slices showed a response significantly different from baseline 40 to 50 min after the tetanus (Fig. 3).

As a negative control for the nonspecific effects of genistein, slices from young rats ($n = 2$) were tetanically stimulated in the presence of 20 μM daidzein, the inactive analog of genistein. Daidzein did not significantly change the magnitude of potentiation over the time 40–50 min posttetanus compared with control solution ($P > 0.31$, data not shown).

DISCUSSION

In this study both nmdaLTP and vdccLTP were measured in the CA3 to CA1 synapse in aged rats, but their pattern of expression differed from young controls. NmdaLTP was smaller, and vdccLTP larger, in the aged animals. Interestingly, the magnitude of the compound LTP (the sum of nmdaLTP and vdccLTP) was similar in both age groups, as the age-related decline in nmdaLTP was compensated for by an increase in vdccLTP. Neither form of LTP reached stable values in aged rats over the time examined, yet plateau levels were reached in young rats. These findings suggest that there may be a compensatory mechanism that maintains constant the overall level of plasticity achievable at a synapse.

Such compensatory aging changes were observed at other synapses. The neuromuscular junction of aged mice have a smaller vesicle pool, but a higher vesicle turnover rate sustains functional transmission (Fahim and Robbins 1982; Robbins 1992). Similarly, an increase in the strength of individual synapses preserves throughput in the aged rat perforant path to dentate gyrus pathway despite a decrease in the number of synaptic contacts (Barnes 1994). It is unknown whether the present results represent a normal process of aging or a response to a pathological condition.

The decreased nmdaLTP observed in 24 mo old rats may represent the culmination of a normal developmental shift in synaptic plasticity from NMDAR to VDCC mechanisms that occurs throughout cortical neurons, with varying time courses. In neocortex, nmdaLTP is present during development, but later declines or is lost completely, with a time course matched to the critical period for experience dependent plasticity for each particular region (Crair and Malenka 1995; Kirkwood et al. 1995; Teyler et al. 1989). In adult neocortex, a large fraction of the remaining LTP is the VDCC form (Aroniadou et al. 1993; Aroniadou and Keller 1995; Komatsu 1994). Another form of NMDAR dependent plasticity, long-term depression (LTD), was found to be developmentally transient in both CA1 (Dudek and Bear 1993; Harris and Teyler 1984) and CA3 (Battistin and Cherubini 1994). A general feature of excitatory cortical synapses may be that during relatively early ages NMDA receptors are abundant and provide for both potentiation and depression of synaptic strength, although at later ages there is a shift toward nonNMDAR mediated mechanisms. Given the shift toward vdccLTP in aged animals, it is quite possible that deficits seen in aged animals are the result of excessive vdccLTP, rather than inadequate nmdaLTP. The data from nimodipine administration in aged animals seems to support this possibility (Disterhoft et al. 1994).

Previous studies of LTP and aging indicated either no change in LTP or a decline with aging. Because none of these studies identified the forms of LTP present, it is unknown to what extent the different forms of LTP were induced by the tetanus parameters employed. It is possible, however, that many of the experiments used tetanus parameters yielding a compound LTP, as even a 100 Hz/1 s tetanus induces a compound LTP (Cavus and Teyler 1996). If so, finding little or no change with age agrees with our findings for a compound LTP.

The present data also support an aging-induced Ca^{2+} dyshomeostasis hypothesis (Khachaturian 1984, 1989, 1994; Landfield 1987). A variety of Ca^{2+} related mechanisms are altered in neurons by aging, including Ca^{2+} influx and extrusion across the plasma membrane, cytosolic buffering, and uptake in organelles (Disterhoft et al. 1994; Gibson and Peterson 1987; Michaelis 1994; Verkhratsky et al. 1994; Villa et al. 1994). As noted, Ca^{2+} current through L-type channels is increased in CA1 pyramidal neurons. Two implications of this increased Ca^{2+} current for neuronal function in aged animals have been proposed: cytotoxic effects of excess intracellular calcium (Landfield 1994) and decreased excitability (Moyer et al. 1992; Thompson et al. 1990). The present findings of an increased vdccLTP in aged rats suggest that aging-related alterations in L-type Ca^{2+} currents may also affect learning and memory more directly through alterations in synaptic plasticity.

These data offer additional support for the existence of two forms of LTP, each of which possesses differing induction requirements and is associated with a different signal transduction pathway. That these two forms of LTP may lead to different cellular responses is suggested by the obser-

FIG. 3. VdccLTP has been shown to activate a tyrosine kinase signal transduction pathway and can be blocked with genistein, a tyrosine kinase inhibitor, or nifedipine, an L-type Ca^{2+} channel blocker. Tyrosine kinase inhibition with 20 μM genistein (■) results in less compound LTP compared with controls (●) in both young (*A*, $n = 6$) and old (*B*, $n = 5$) animals. However kinase inhibitor was much more effective in blocking potentiation in old than young animals ($P > 0.02$). That two drugs are affecting same signal transduction mechanism is shown by absence of additional blockade when both genistein and nifedipine are employed (▲, $n = 5$ each). Also, for both ages effect of genistein was not significantly different from effect of VDCC blocker nifedipine (data in Fig. 1). Blockage of NMDA receptors by APV and inhibition of tyrosine kinases by genistein together prevents potentiation (◇; $n = 3$ each). Mean ± SE of percentage change from baseline fEPSP slope for each group is shown every 2 min. *Insets*: representative fEPSPs from one slice in each group taken 5 min before (1) and 45 min after (2) tetanus. Scale bar: 0.5 mV, 5 ms.

vation that the activation of different calcium signaling pathways may lead to differential gene regulation in the nucleus (Bading et al. 1993; Ghosh and Greenberg 1995). Such potential differential gene regulation may have different functional and behavioral effects (Cavus and Teyler 1996). For example, NMDA receptor antagonism is ineffective in certain forms of learning (Saucier and Cain 1995), supporting the idea that learning, like LTP, is not dependent on a single underlying mechanisms.

Although synaptic plasticity and LTP in particular is a strong candidate as a mnemonic mechanism, the relationships between specific forms of synaptic plasticity and the formation of memory remains unclear. Although the compound LTP induced in response to a 200-Hz tetanus was not altered by aging, memory formation may yet be affected. The properties of nmdaLTP and vdccLTP suggest that they serve differing functions and therefore aging-related alterations in their induction or expression may explain learning and memory deficits in aged animals. Elucidation of the physiological roles of nmdaLTP and vdccLTP may provide the basis for a rational program of therapeutic intervention against aging-induced memory deficits.

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