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Nimodipine Facilitates Learning and Increases Excitability of Hippocampal Neurons in Aging Rabbits

John F. Disterhoft, L. T. Thompson, James R. Moyer, Jr., and Mira Kowalska

Department of Cell, Molecular, and Structural Biology, Northwestern University Medical School, Chicago, IL, U.S.A.

Summary: A series of preclinical experiments have used eyeblink conditioning and the in vivo and in vitro rabbit hippocampus for behavioral, neuroanatomical, neurophysiological, and biophysical analyses of associative learning. One goal of these experiments is to understand how neuronal excitability changes during learning in young brain, and how neurons in aging brain may be impaired in their ability to produce such changes. A second goal of these experiments, focused on the role of calcium-mediated processes in learning, has been to investigate the potential contribution of nimodipine in enhancing learning in aging subjects. We have concentrated much of our recent effort on the hippocampus, known to be important for learning in mammalian brain and very much affected by aging and Alzheimer's disease. Hippocampal ablation was shown to block acquisition and/or extinction in eyeblink tasks, most prominently in trace conditioning. Extracellular recordings in vivo have demonstrated increased excitability of hippocampal neurons to the conditioned stimulus (CS) in eyeblink conditioning. Analyses of cellular events underlying this increased excitability demonstrated a conditioning-specific reduction in the post-burst afterhyperpolarization (AHP) of CA1 neurons in hippocampal slices. The afterhyperpolarization is a postsynaptic response generated by an outward calcium-dependent potassium current and is an important determinant of neuronal excitability. This hyperpolarizing response is increased in aging hippocampal neurons, presumably as a result of increased intracellular calcium levels in aging neurons, thus reducing their excitability and their ability to show adaptive change during associative learning. The calcium channel blocker nimodipine facilitates acquisition of trace eyeblink conditioning in the aging rabbit, as in other learning tasks. Convergent data suggest that this learning enhancement may also be mediated by changes in hippocampal neuronal excitability. These excitability increases results from reduced calcium influx through voltage-gated calcium channels, and a secondary post-burst reduction in the AHP. The relevance of our findings to potential clinical applications in aging and/or Alzheimer's disease is discussed. **Key Words:** Afterhyperpolarization—Aging—Alzheimer's disease—CA1—Calcium channel antagonist—Eyeblink conditioning—Hippocampus—Nimodipine.

Address correspondence and reprint requests to Dr. J. F. Disterhoft, Department of CMS Biology, Northwestern University Medical School, 303 E. Chicago Ave., Chicago, IL 60611, U.S.A.

Eyeblink conditioning (20) and various rabbit hippocampus experimental preparations have been used in aging and young animals in our experimental program. We have also begun work doing eyeblink conditioning in the human to parallel our animal experiments. These studies and their theoretical rationale have recently been reviewed extensively (11,15,17,36). We will therefore focus on the highlights of our experiments and on recent developments in this paper.

An important feature of our approach has been to use a behavioral paradigm that is dependent upon the hippocampus for its acquisition. We have used trace eyeblink conditioning in which a tone conditioned stimulus (CS) precedes an air puff unconditioned stimulus (US) by 500 msec, and in which rabbits (and humans) must form a short term "memory trace" of the CS occurrence in order to time their conditioned eyeblink so as to minimize the air puff impact on every trial (Fig. 1). Complete hippocampal ablation blocks acquisition of trace eyeblink conditioning in this task in rabbits (28) while smaller lesions produce less severe impairments. Our interest in utilizing a hippocampally dependent conditioning task arises from the fact that both lesion and in vivo recording experiments in animals have demonstrated a profound involvement of the hippocampus in eyeblink conditioning and other associative learning tasks (2,5,33) and that bilateral hippocampal damage in the human leads to profound memory loss (30,32,33,42). Finally, the hippocampus is known to be especially affected anatomically and physiologically in the aging brain and in disease states associated with aging (4,39). This fact is of particular importance within the context of studies of agents such as nimodipine which may be particularly useful in treating learning deficits associated with aging and/or Alzheimer's disease.

Several of our recent experiments have focused on characterizing the effects of nimodipine (31) on age-impaired associative learning. We also attempted to analyze potential cellular neurobiological substrates for those effects. We were led to our experiments with nimodipine in aging brain as a result of an ongoing series of experiments which we had done to analyze cellular substrates of eyeblink conditioning in hippocampus using the hippocampal brain slice technique (13,14,16). Our interest was to study the cellular events underlying the increased excitability of hippocampal neurons observed during and after associative learning. To do this, we first trained animals in our eyeblink paradigm and then prepared in vitro hippocampal slices to evaluate biophysical changes in hippocampal neurons which occurred during and after classical conditioning. This preparation has allowed us to evaluate cellular alterations which we know *a priori* are local to the hippocampus at the time of their analysis and are not secondary reflections of alterations elsewhere in the conditioned reflex arc. An important observation which we have made is that the post-burst afterhyperpolarization is reduced in hippocampal CA1 neurons after eyeblink conditioning (7,9,13). This voltage response, which hyperpolarizes the neuronal membrane relative to its resting level after a series of action potentials and regulates burst firing activity of hippocampal pyramidal neurons, is generated by a calcium-activated potassium conductance, I_{AHP} (1,22,25,34). This outward potassium conductance is activated by calcium that flows into the neuron with the sustained depolarization during a burst of action potentials (7,22). We have consistently observed a reduction in this afterhyperpolarization (AHP) after learning (3,7,9,13). We have suggested that this AHP reduction is an important contributor to increased hippocampal excitability, i.e., increased firing to the tone CS as it becomes behaviorally significant, a finding consistently observed in eyeblink conditioning over the course of associative learning (2,5).

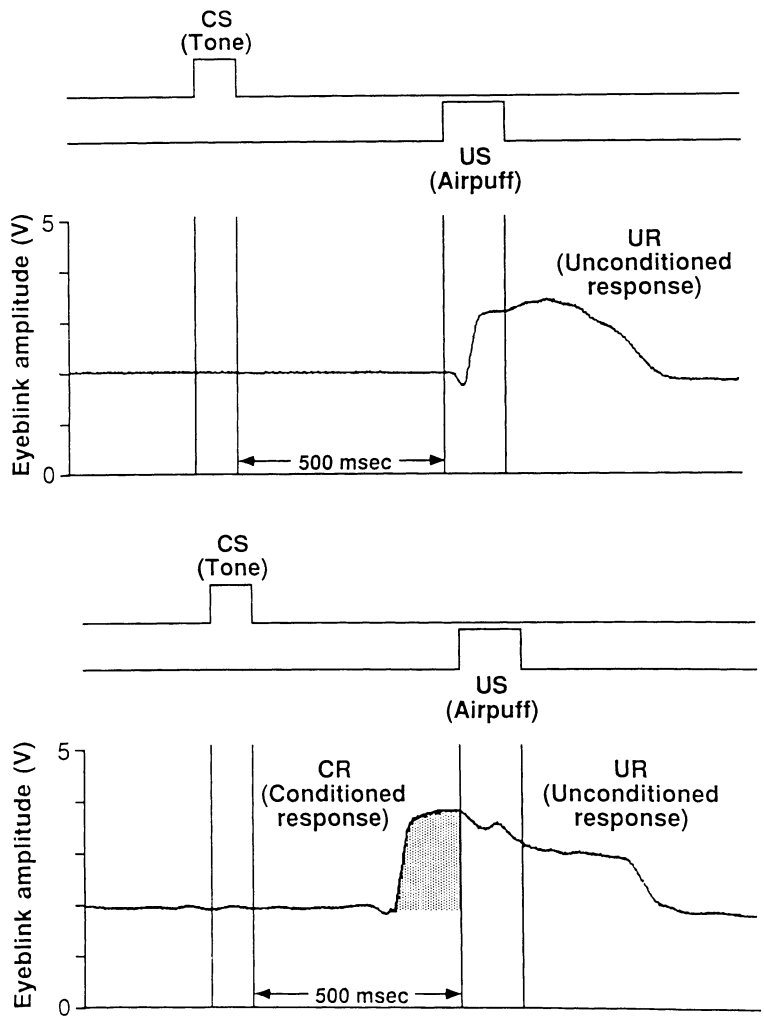

FIG. 1. The trace eyeblink conditioning paradigm used with both rabbits and humans. A 100 msec pure tone conditioned stimulus (CS) is presented with binaural headphones. After a 500 msec interstimulus trace interval, the 150 msec air puff unconditioned stimulus (US) is presented to the cornea of the eye. The term "trace interval" was introduced by Pavlov and describes the fact that the subject must form a short latency memory or "stimulus trace" of the CS in order to successfully time the conditioned eyeblink response which serves to minimize the US impact on the eye. In rabbits, extension of the third eyelid (nictitating membrane response) is measured in our laboratory with a noninvasive phototransistor that detects the increased reflection of light from a light emitting diode during the blink. In humans, eyeblinks are measured with the same noninvasive system. Eyeblink responses on two individual trials in a human subject are indicated. Early in training (upper panel), unconditioned responses occur to airpuff onset but no eyeblink occurs to tone CS presentation. Later in training, conditioned eyeblinks occur to the tone presentation prior to airpuff US presentation. These conditioned responses occur with greater frequency, shorter latency, and larger amplitude as conditioning proceeds (12).

The connection between the AHP reduction observed during learning in young animals and the cellular changes that may underlie learning deficits in the aging brain is straightforward. The post-burst AHP is markedly increased in both amplitude and duration in hippocampal CA1 neurons from aging rabbits (29; Fig. 2). When the observation was initially made in rats that AHP duration was increased in aging CA1 neurons, Landfield

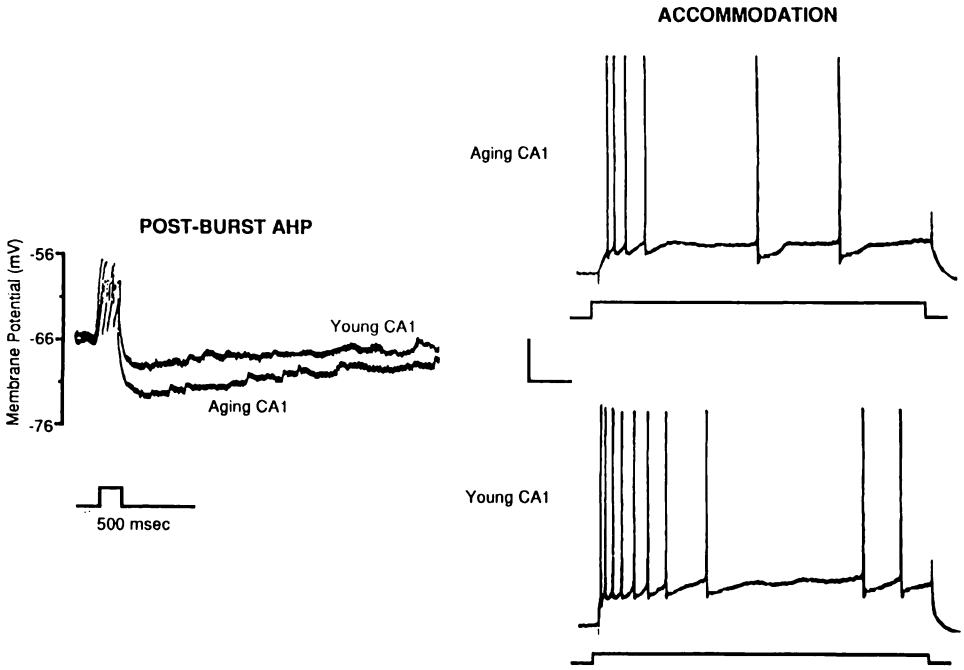

FIG. 2. Aging CA1 pyramidal neurons were less excitable than young CA1 neurons. The post-burst AHP was larger both in amplitude and duration in cells from aging rabbits **(left panel).** Accommodation (or spike frequency adaptation) to a long depolarizing current injection was greater in aging **(top right)** than young neurons **(bottom right).** Calibration for right panel, 20m V, 1 nA, 100 msec. Adapted from ref. 29.

and Pitler (27) suggested that this increase would reduce hippocampal excitability and potentially make learning more difficult. Given the importance of AHP reductions in regulating the increases in neuronal excitability that occur during learning, we reasoned that it might be possible to use a compound that would artificially reduce the post-burst AHP in aging rabbit hippocampus to speed the learning rate. To evaluate this possibility we used nimodipine, a calcium channel blocker that crosses the blood-brain barrier with relative ease (31,38). In our first study we found that when administered intravenously nimodipine markedly enhanced the learning rate of aging rabbits, causing them to acquire the trace eyeblink conditioned response at the same rate as young controls and markedly faster than aging controls (10; Fig. 3). Nimodipine had no significant enhancing effect on learning rates in young rabbits nor did it increase nonassociative responses to the tone CS. We are currently completing a dose/response curve to determine an effective dose range of intravenous nimodipine in aging rabbits (24). It appears that at a range of doses between 0.5–5 μg/kg/min intravenous nimodipine effectively enhances eyeblink conditioning in relation to vehicle controls. We have not yet analyzed the serum concentrations of nimodipine in these ongoing studies.

We have done several neurophysiological studies in an attempt to determine if nimodipine causes alterations in hippocampal excitability which could contribute to the enhancement of learning that we have observed. In the first, single CA1 neurons were recorded in awake young and aging rabbits (35), prepared as for eyeblink conditioning. We observed that with intravenous administration nimodipine caused an age- and con-

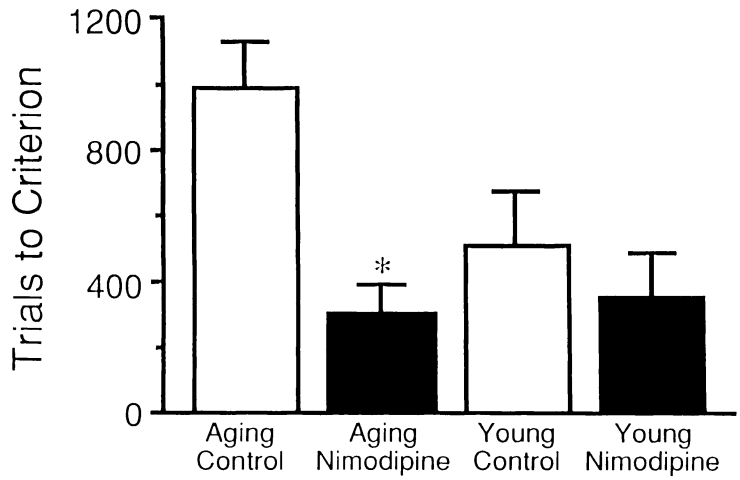

FIG. 3. Nimodipine facilitated acquisition of trace eyeblink conditioning in aging rabbits. Note that aging control rabbits required more trials to reach the criterion of 8 CRs in any block of 10 trials than did young or aging nimodipine-treated rabbits. Adapted from ref. 10.

centration-dependent enhancement of the spontaneous firing rate of pyramidal neurons. Nimodipine caused a markedly greater effect on neuronal excitability in aging than in young rabbits (Fig. 4). The dose that was most effective, 1 μg/kg/min, was the same as that used in our earlier study to enhance learning rates in aging rabbits (10). Nifedipine, a dihydropyridine that does not cross the blood-brain barrier as readily as nimodipine (38), caused no significant change in spontaneous firing rate. Similarly, at a wide range of doses sufficient to control for the possibility that enhanced blood flow caused the excitability changes produced by nimodipine, the piperazine-type calcium antagonist flunarizine also caused no alteration in firing rate.

In the final series of studies, we used the hippocampal slice preparation to determine if nimodipine increased CA1 pyramidal neuron excitability in vitro in a preparation where blood flow could have no possible contribution to effects observed (18,29). We used two measures of excitability, the post-burst AHP and accommodation (or spike frequency adaptation), in these studies. At relatively high concentrations nimodipine (10 μ*M*) caused a reduction of the post-burst AHP in both young and aging CA1 pyramidal neurons, although the effect was considerably larger in the aging neurons. What was particularly interesting is the fact that at concentrations as low as 100 n*M* nimodipine caused a significant reduction of the post-burst AHP in aging but not in young CA1 neurons (Fig. 5). This effect was obvious both in reductions in the peak amplitude and in the integrated area of the AHP. It should be noted that nimodipine reduced the AHP in aging neurons to within the range observed in young neurons. Nimodipine at relatively high doses (10 μ*M*) also reduced accommodation in both young and aging neurons. But nimodipine was effective in significantly reducing the amount of accommodation in concentrations as low as 10 n*M* only in aging neurons (Fig. 6). In voltage-clamped dissociated hippocampal pyramidal neurons, nimodipine blocked a significant proportion of inward calcium currents, while BAY K 8644 enhanced inward currents (6). It is clear that nimodipine's effects on the post-burst afterhyperpolarization and accommodation

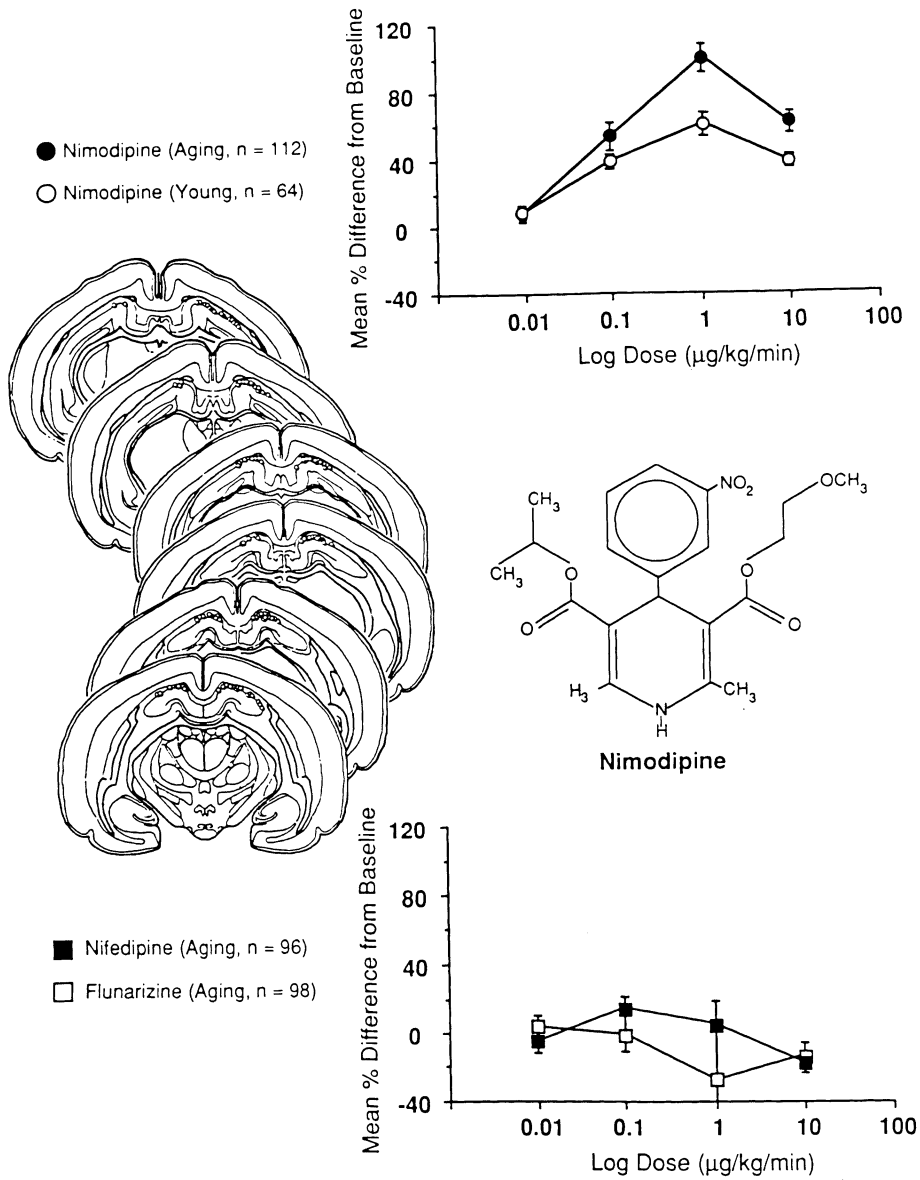

FIG. 4. Nimodipine increased excitability of hippocampal neurons recorded in vivo in conscious rabbits. The position of recording sites in CA1 of hippocampus. Dose-dependent effects of nimodipine on spontaneous activity of single hippocampal CA1 neurons recorded in vivo in aging (●) and young (○) rabbits. Nimodipine had a maximal effect at the dose which facilitated learning in aging rabbits (1.0 μg/kg/min). At all doses tested, the effect was larger in aging rabbits **(upper right).** The chemical structure of nimodipine is shown. At the same range of doses nifedipine and flunarizine had no effect on CA1 pyramidal neuron firing rate, indicating that the nimodipine effect was mediated by direct actions on neurons, not via changes in cerebral blood flow **(lower right).** Adapted from ref. 35.

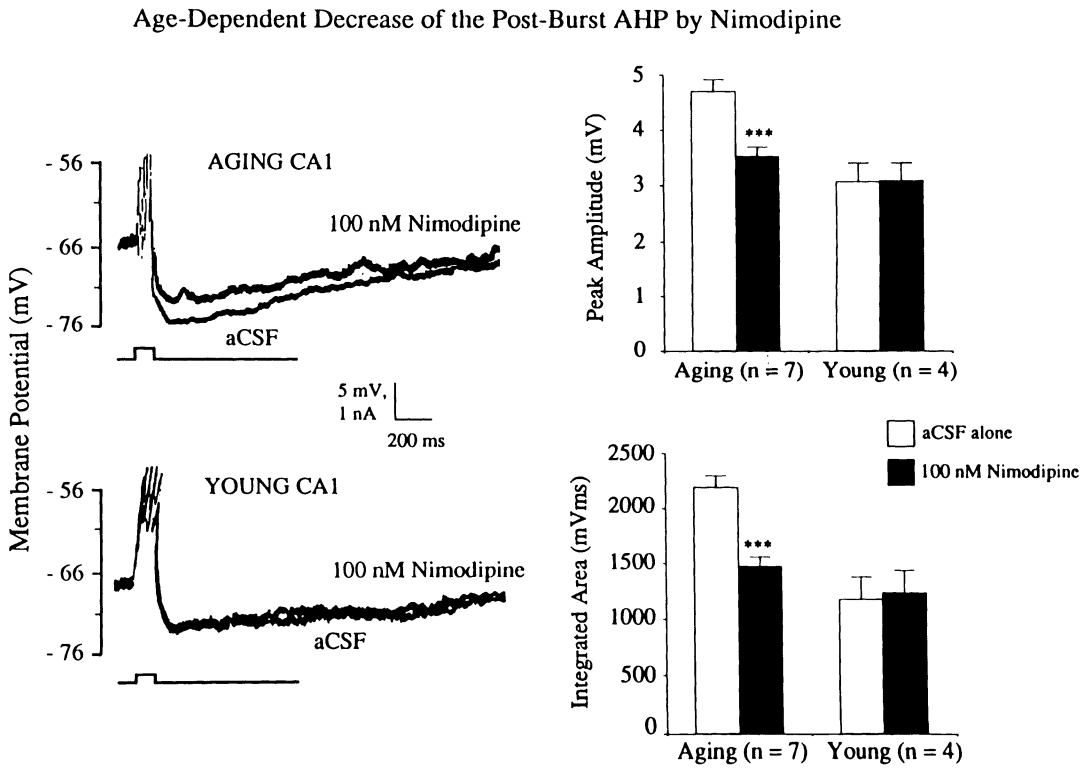

FIG. 5. Nimodipine at a concentration of 100 n*M* caused a significant reduction in the post-burst afterhyperpolarization in CA1 neurons from aging but not young rabbits. The reduction was present both in the integrated area of the afterhyperpolarization (AHP) (a reflection of increased duration) as well as in the peak amplitude of the response. Scale in left panel, 5 mV, 1nA and 200 msec. Adapted from ref. 29.

could well be due to secondary consequences of modulation of calcium influx via voltage-gated L-type calcium channels.

CONCLUSIONS

We have described a series of studies focused on investigating the role of hippocampal neurons in the formation of an associatively learned eyeblink response. It is known that hippocampal neurons show increased excitability during the learning of this task, i.e., they fire more vigorously to a tone conditioned stimulus as it gains behavioral significance. Our analyses of CA1 neurons in hippocampal slices from conditioned rabbits have demonstrated that an important cellular substrate for this excitability change is a reduction in a post-synaptic response mediated by voltage-dependent calcium influx occurring during action potentials. This post-burst calcium-dependent afterhyperpolarization is increased in hippocampal neurons in aging rabbits, making it more difficult for them to learn the eyeblink response. The increase in the afterhyperpolarization may result from increased intracellular calcium levels or from altered calcium buffering in aging neurons. The afterhyperpolarization increase is consistent with the so-called "calcium hypothesis of aging" (23,26).

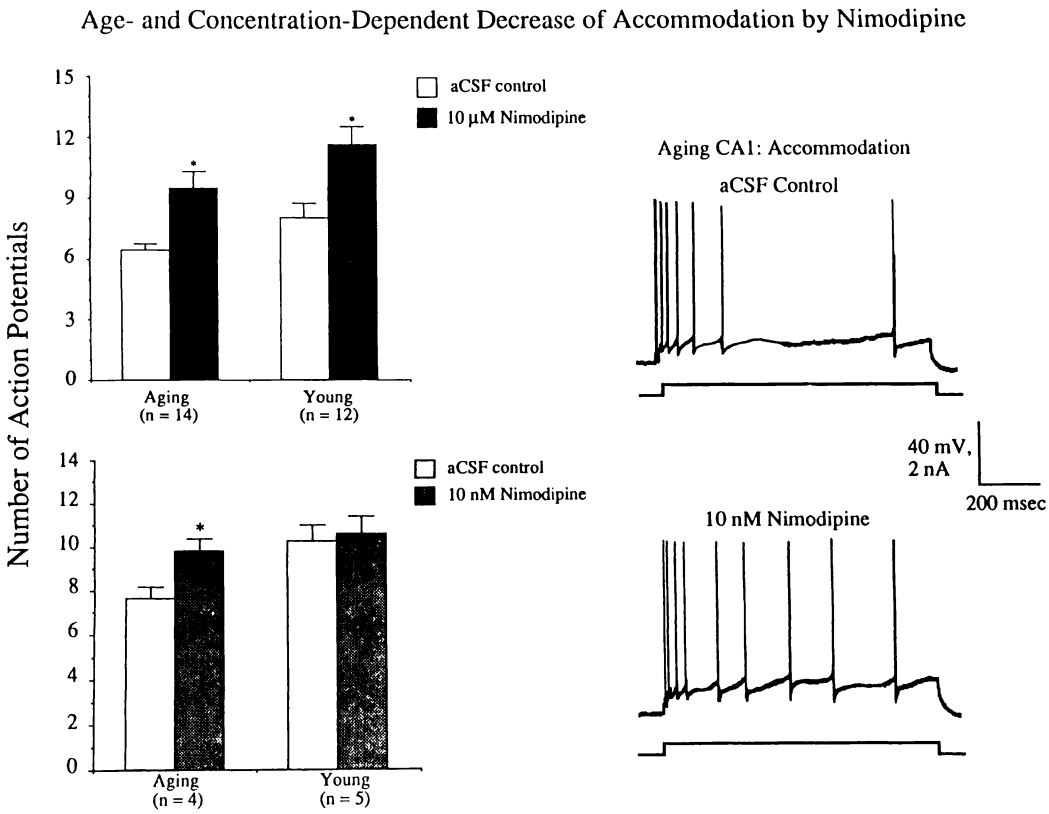

FIG. 6. Nimodipine reduced spike frequency adaptation or accommodation at high (10 μM) concentrations in both aging and young CA1 neurons. But nimodipine at low (10 n*M*) concentrations was effective only in reducing accommodation in aging neurons. An example of this accommodation decrease in an aging neuron by 10 n*M* nimodipine, with functional enhancement of neuronal excitability, is shown in the panel on the right. Adapted from ref. 29.

Nimodipine is effective in enhancing eyeblink conditioning learning rates in aging rabbits. Our hypothesis is that the learning rate enhancement may be mediated by nimodipine's ability to block L-type calcium channels and therefore to reduce calcium influx during neural activity. Such a reduction should reduce the afterhyperpolarization, enhance neural excitability, and therefore increase learning rate. We have summarized in vivo and in vitro neurophysiological recording data from hippocampal neurons which support this hypothesis. Spontaneous firing activity is increased in vivo and the afterhyperpolarization and accommodation are decreased in vitro by nimodipine in an age- and concentration-dependent fashion. These data are consistent with our hypothesized mechanism of action of the drug. They also suggest that an important locus of action of nimodipine as a learning enhancer in aging brain may be the hippocampus.

Aging humans show behavioral deficits when tested using 500 msec trace eyeblink conditioning (12). Eyeblink conditioning appears to have many advantages for the study of the neurobiological causes of learning deficits occurring in some aged humans and animals (21,37,40,41). In particular, the appearance of aging-related deficits in eyeblink

conditioning in rabbits parallels that in humans: in both species these impairments begin in middle age (30 months for rabbits; 40 years for humans). Unlike many other tests of learning and memory, eyeblink conditioning does not depend upon nonmnemonic cognitive capacities that are also at some risk in aging such as language, problem-solving, and visuospatial abilities. Therefore, eyeblink conditioning may provide a relatively pure measure of a specific learning capacity. Another consideration is that eyeblink conditioning is impaired in subjects with temporal lobe dysfunction (8) and in Alzheimer's patients, a group with known hippocampal degeneration (19). Hence, eyeblink conditioning in rabbits would appear to be an excellent animal model with which to evaluate the mechanisms of, and therapeutic interventions for, learning deficits in the aging human population as well as in Alzheimer's patients. We have a clinical trial ongoing to test the effects of nimodipine on the eyeblink conditioning learning deficits which we have observed in normal aging subjects. This kind of approach obviously can also be applied to patients with Alzheimer's disease or age associated memory impairments.

We suggest that our research strategy, which combines cellular and subcellular with behavioral analyses in a powerful animal model of associative learning, may be fruitful in understanding the neurobiological alterations that occur in aging brain (15,36). Based on a thorough understanding of these changes in our animal model, we should be better able to optimize the opportunity to develop pharmacological agents to revitalize learning abilities in aging and/or diseased brain.

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Discussion

R. Tsien: I like the whole spectrum of approaches you have used. Is it possible to affect the learning by other agents that effect the AHP to the same degree or in much the same way that nimodipine does? Because what you are saying, if you boil it all down, it seems like you have targeted one particular cellular pathway to making more action potentials happen to induce an LTP-like phenomena that may underlie the learning. One might think then that a clinically unuseful, but experimentally inciteful, agent could mimic the effect.

J. Disterhoft: Your point is well taken. But we have not yet explored the behavioral and neurophysiological effects of other agents which may affect the AHP. For example, other Ca^{2+} channel blockers, like verapamil and diltiazem, may be useful. Toxins, such as charybdotoxin, that directly effect the AHP would also be predicted to enhance learning rate. Unfortunately, we haven't done these experiments at this point in time. You ask an excellent question.