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NIMODIPINE IMPROVES LEARNING AND SENSORIMOTOR BEHAVIORS IN AGING MAMMALS

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Introduction

Two troubling concomitants of aging for many individuals are a reduction in sensorimotor capacity and an impairment of learning and memory, which often occur even in "normal" aging. An important common factor associated with both age-related physiological deficits and with learning and memory deficits is the perturbation of calcium metabolism in neurons and other cells throughout the body (Khachaturian, 1984; Landfield, 1987). We have used nimodipine, a dihydropyridine calcium channel blocker, to modulate calcium action in aging rabbits, and have observed marked facilitation of associative learning (Deyo et al., 1989a) and alterations in open field behaviors, interpretable as an improvement of sensorimotor responsivity (Deyo et al., 1989b). In our experiments, aging rabbits given nimodipine behave more like young controls than their age-matched cohort group. Studies using other species and behavioral tasks also indicate that nimodipine facilitates learning tasks and sensorimotor tests which may have good face validity when generalized to humans. In general, learning tasks used are mediated by hippocampus, a structure known to be especially affected by Alzheimer's disease (Van Hoesen and Damasio, 1987) as well as by aging (Geinisman et al.,1986; Barnes, 1988).

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Eyeblink Conditioning as a Model for Studying Learning Deficits in Aging

Eyeblink or nictitating membrane conditioning has been adapted as a "model behavioral system" for use in the analysis of the neural substrates of learning by several laboratories (Disterhoft et al., 1977; Thompson et al., 1976). Among its advantages are the relative simplicity of the behavioral paradigm, the excellent control procedures available, the fact that associative learning is analyzed, the ease of conditioned and unconditioned stimulus application and control, the ease of precise behavioral and neurophysiological measurement, and the extensive body of behavioral data which are available for this preparation (Gormezano et al., 1987).

Eyeblink conditioning appears to have many advantages for the study of the neurobiological causes of learning deficits which occur in some aged humans and animals (Woodruff-Pak & Thompson, 1985; Thompson, 1988). Eyeblink conditioning is impaired in both older humans and animals (Braun and Geiselhart, 1959; Graves & Solomon, 1985; Solomon et al., 1989; Woodruff-Pak & Thompson, 1988). In particular, the appearance of age-related impairments 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, eye-blink 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 (Daum et al., 1991) and in Alzheimer's patients, a group with known hippocampal degeneration (Finkbiner and Woodruff-Pak, 1991). 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.

Nimodipine Facilitates Hippocampally-Medicated Learning in Aging Mammals

Nimodipine is a dihydropyridine which is a potent calcium channel blocker (Scriabine et al., 1985; Janis et al, 1987). Its positive effects on learning were first noted in a preliminary study in older persons with chronic cerebrovascular disorders (Bono et al., 1985). For the theoretical reasons noted in the accompanying chapter (Thompson et al., 1991) we tested the effect of intravenous nimodipine on trace eyeblink conditioning in a group of young (3 months) and aging (36+ months) rabbits. Age-matched control rabbits received the vehicle solution intravenously. The paradigm we used employed a short 6 kHz tone as a conditioned stimulus (CS) followed with presentation of a mild corneal air puff sufficient to elicit an eyeblink as unconditioned stimulus (US). A 500 msec interval intervened between the tone and air puff. This interstimulus interval is termed a "trace" interval, since the task of the rabbit is to retain a stimulus trace of the tone CS in order to

successfully predict the time of onset of the corneal air puff and blink at the appropriate time. Rabbits begin to give eyeblink conditioned responses (CRs) during the trace interval, just before the onset of the air puff, as learning proceeds. The conditioned eyeblink responses tend to reduce the impact of the air puff on the cornea as the rabbits learn to give larger and shorter latecy conditioned eyeblinks on a large percentage of trials. 80 training trials were given daily for a maximum of 15 training sessions.

We found that intravenous infusion of nimodipine at 1 μg/kg/min markedly facilitated acquisition of the trace eyeblink conditioned response in aging rabbits (Deyo et al., 1989a; see Figure 1). In fact, they reached a criterion of 8 CRs in 10 trials slightly faster than did young animals receiving the same nimodipine dose or than young animals receiving vehicle. As was anticipated, aging control rabbits took much longer to reach criterion than did the young control rabbits. Training was terminated for many of the aging control rabbits that did not reach criterion within 15 training days. Pseudoconditioning control animals, for whom the tone CS and air puff US were given randomly in time in an explicitly unpaired fashion, showed no tendency to give eyeblink CRs to the tone, i.e., nimodipine did not cause nonspecific sensitization to the presentation of the stimuli. There was also no difference in the size of the eyeblink responses to the tone (conditioned responses) or to the air puffs (unconditioned responses) between the nimodipine and control groups. All of these behavioral features suggest that nimodipine was acting by enhancing neural function involved in forming the association between the tone and air puff, rather than altering responsivity to the tone or air puff stimuli themselves. Long interval trace eyeblink conditioning is known to be dependent upon the hippocampus for its successful acquisition (Solomon et al., 1986; Moyer et al., 1990). As is explained below and in our companion chapter (Thompson et al., 1991), our working hypothesis is that nimodipine acts by increasing the excitability of neurons in the hippocampus. Since we have administered nimodipine systemically in our experiments thus far, brain regions other than hippocampus could also be involved.

In a follow-up study, we showed that nimodipine added to the food supply of aging rabbits (860 ppm for one month) also enhanced the acquisition rate in the trace eyeblink paradigm (Straube et al., 1990). The learning rate enhancement was not as dramatic in the oral nimodipine study, possibly because the serum and brain nimodipine levels were not elevated to the same degree as in our previous intravenous application study. A dose/response study using intravenous drug administration in rabbits is currently being carried out in our laboratory to determine the optimal levels of serum and brain nimodipine for learning facilitation. Preliminary evidence suggests that there may be an inverted U-shaped dose/response curve with levels of nimodipine higher than 5 μg/kg/min inhibiting rather than enhancing learning rate. We are also observing that nimodipine enhances acquisition using a more stringent 80% CRs per 80 trial training session criterion, in addition to our earlier 8 of 10 CRs criterion.

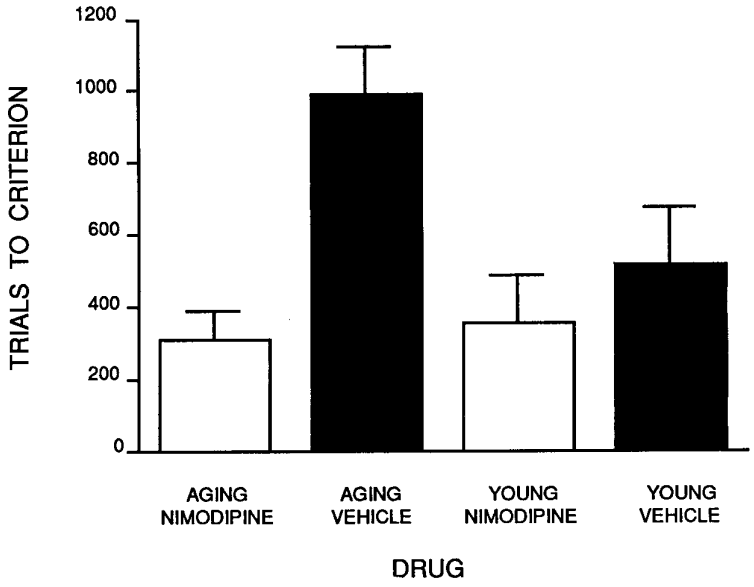

Figure 1. Nimodipine enhances trace eyeblink conditioning in aging rabbits. Summary of mean trials to criterion (8 CRs in any block of 10 trials). Subjects received 1.0 μg/kg/min nimodipine or vehicle injections. Trace conditioning consisted of a 100 ms tone conditioned stimulus (CS) followed by a 500 ms trace period during which no stimulus was presented, followed by a corneal air puff (UCS: 150 ms, 2.5 psi). An unconditioned response (UCR) was an eye-blink occurring in response to the UCS. A conditioned response (CR) was any response occurring after CS onset but prior to UCS onset. Nimodipine significantly facilitated eyeblink conditioning of aging animals ($F(1,20)= 10.51$, $p < .005$), without affecting amplitude of CRs or UCRs. Bars: mean ± SEM (n=6 for each group). (Deyo et al, 1989a)

Nimodipine also appears to facilitate learning tasks in aging species other than rabbits. Water maze learning is facilitated in aging rats maintained for 49 days on food containing only 275 ppm nimodipine (Schuurman and Traber, 1989). Similarly, delayed matching to sample performance is enhanced in aging monkeys given oral nimodipine before the training session (Sandin and LeVere, 1990). Since the hippocampus plays such a central role in the learning deficits seen in Alzheimer's disease and in the Age Associated Memory Impairment (AAMI; Crook et al., 1986) syndrome, it is of particular interest that the behavioral tasks used in these two studies are likely to be hippocampally-dependent. These tasks, like trace eyeblink conditioning in rabbits (Moyer et al., 1990), depend upon

hippocampus for their successful acquisition (Squire, 1986). As described in the accompanying paper (Thompson et al, 1991), hippocampus has a high concentration of dihydropyridine binding sites. So the specific target of nimodipine's actions in all three research lines could well be the hippocampus.

Mechanisms for Nimodipine's Learning Enhancement

There are two obvious candidate mechanisms for the enhancement of learning by nimodipine. First, nimodipine may enhance cerebral blood flow by inducing cerebral vasodilation through blockade of calcium channels in vascular smooth muscle. Several of the substances which enhance learning in old animals are thought to act by this mechanism (Hock, 1987). And the concentrations of nimodipine we used are known to increase cerebral blood flow in unanesthetized rabbits (Haws et al., 1983). Flunarizine, a piperazine calcium channel blocker which is a potent vasodilator (Sugita et al., 1987), had no effect in old rats learning the water maze task described above (Traber, personal communication). This would argue against vasodilation *per se* as the major cause of the learning facilitation we observed. In addition, as discussed in our companion paper in this volume (Thompson et al., 1991), nimodipine increased hippocampal single neuron firing rate in an aging- and dose-dependent fashion in conscious, unanesthetized rabbits. Flunarizine, at doses quite sufficient to enhance cerebral blood flow, had no effect (Thompson et al., 1990).

The second possible mechanism for nimodipine's action in learning, and the one which motivated our initial interest in studying this compound, is direct blockade of neuronal calcium channels. The afterhyperpolarization (AHP) which follows a burst of action potentials is reduced in hippocampal pyramidal neurons in a conditioning-specific fashion (Disterhoft et al., 1986; Coulter et al., 1989). This reduction is correlated with behavioral acquisition of the eyeblink conditioned response in rabbits (Disterhoft et al., 1988b); occurs after trace eyeblink conditioning in hippocampal CA1 pyramidal cells but not dentate granule cells (deJonge et al., 1990); and is associated with an alteration in NMDA mediated synaptic transmission (LoTurco et al., 1988). We have argued that this alteration is localized to the hippocampus, as it occurs in hippocampal slices separated from their normal afferent and efferent connections (Disterhoft et al., 1988a). The reduction also appears to be postsynaptic, as we have demonstrated it with intracellular current injection and in the absence of sodium spike-dependent synaptic transmission (Coulter et al., 1989).

The AHP is known to reflect a calcium-dependent outward potassium current (Lancaster & Adams, 1986) and is presumed to control firing rate in hippocampal and neocortical pyramidal cells in which it is prominent (Hotson & Prince, 1980). The functional consequence of a reduced AHP after conditioning would be to increase the excitability of hippocampal neurons. *In vivo* studies of single hippocampal pyramidal neurons have demonstrated that large percentages of these neurons show increased

excitability, i.e., increased firing rate to the tone CS, after conditioning (Berger et al., 1983; Akase et al., 1988). The AHP reduction is likely to be one cellular substrate for this increased excitability (Disterhoft et al., 1986).

The relevance of AHP reductions during learning in young adult to learning deficits in aging subjects may be rather direct. Landfield and Pitler (1984) have demonstrated that the AHP is prolonged in hippocampal CA1 neurons from aged rats. We have replicated this observation in CA1 of the aging rabbit (Moyer et al., 1991). Landfield's group has also shown that elevation of plasma magnesium (a competitive inhibitor of calcium) improves reversal learning in both aged and young rats (Landfield et al., 1986). It is conceivable that one factor in the learning deficits in aging animals is a relative inability to reduce the AHP at the cellular level. As discussed in the accompanying chapter (Thompson et al., 1991), we have demonstrated that nimodipine reduces the AHP and accomodation, two indices of cellular excitability, in CA1 neurons in hippocampal slices prepared from aging rabbits; and that nimodipine blocks high-threshold, non-inactivating calcium currents in acutely dissociated hippocampal neurons from guinea pig hippocampus. Thus it seems likely that nimodipine could be acting to enhance learning rate in aging subjects by directly reducing the AHP which is abnormally large in neurons in aging brain.

Nimodipine Alters Sensorimotor Performance in Aging Rabbits and Rats

Aging rabbits that received oral nimodipine and were tested for eyeblink conditioning (Straube et al, 1990) were also evaluated for their performance in an "open field" (Deyo et al., 1989b). In our studies, the open field was a flat space divided into squares with walls on two sides. The experimenter, blind to the treatment condition of the aging rabbits, placed the rabbits onto the open field at the same position for five successive days. Recall that rabbits are prey animals. Thus it is not suprising that young rabbits, when placed on the open field, tend to stay to the border of the open field next to the walls, not move around too much, and spend considerable time sitting, grooming and observing their environment (Figure 2). Aging control rabbits, on the other hand, wander somewhat aimlessly around the open field. Their tendency to expose themselves to the center of the open space, as well as to move around a lot, would have made them easy prey in the wild (Figure 2). Aging rabbits who received nimodipine, on the other hand, behaved very much like young control rabbits (Figure 2). The open field test is somewhat difficult to classify, as it certainly appears to have components of general cognitive functioning. But it also appears to be a test of sensorimotor skill and level of alertness. We have chosen to interpret our data more simply as a test of sensorimotor skill.

A more extensive evaluation of the effects of oral nimodipine on a variety of sensorimotor tasks, as well as open field behavior, was done in aging rats by Schuurman, Traber and their associates (Schuurman and Traber, 1989). In general, they found that aging rats maintained on a diet including nimodipine were considerably better than their age-matched controls on tasks such as crossing a small horizontal rod, crossing a wide

bridge, and pole climbing. An ingenious and objective evaluation of stepping pattern was used in which rats' feet were dipped in developing fluid and then allowed to walk in an alley in which undeveloped photographic paper had been placed. The aging nimodipine rats showed a markedly younger looking walking pattern than their age-matched control cohorts when the photographic paper was developed. The behavior of rats, a foraging species, is the opposite of rabbits when placed in the open field, i.e., young rats tend to explore and move around a lot while aging animals tend to sit passively. Nimodipine caused the aging animals to behave more like young controls. Finally, in a collaborative study with Gispen's laboratory, it was shown that aging rats receiving oral nimodipine (860 ppm) had improved gait patterns, enhanced sensory and motor conduction velocities

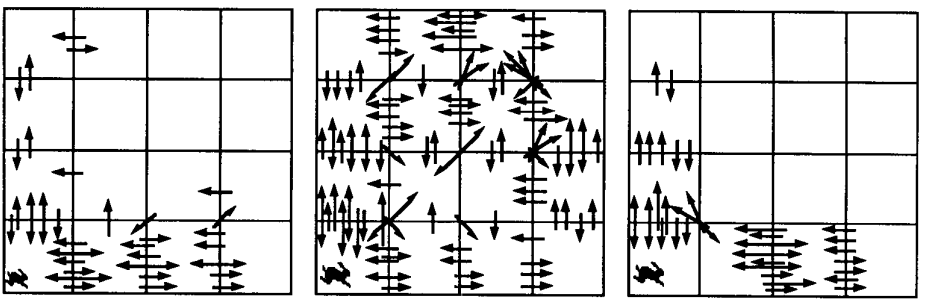

Figure 2. Examples of activity patterns shown on one testing day for a rabbit in each of the three groups. The rabbit symbol denotes the square where the test animal was placed on each of the five successive days on which observations were made. All observations were made double blind. (Deyo et al., 1989b)

in their sciatic nerves, and increased fiber density in the sciatic nerve as compared to controls (Gerritsen van der Hoop et al., 1989). The experimental and control rats in this study werre chosen to exhibit impaired walking patterns when the study began. This observation provides one physiological substrate for the improved behavioral performance of the animals which received nimodipine.

Do Our Studies in Aging Rabbits Generalize to Humans?

We have extensively investigated the cellular mechanisms of learning and of aging-related deficits in learning in the rabbit. Because the hippocampus is clearly implicated in the learning deficits which are a prominent symptom of Alzheimer's disease (van Hoesen et

al. 1986; van Hoesen and Damasio, 1987) and of Age Associated Memory Impairment (Crook et al., 1986), we have used a hippocampally-dependent task, trace eyeblink conditioning, in our studies. But an obviously unanswered question is whether our animal studies generalize to the aging human population. This is a difficult and important issue which is difficult to resolve definitively because we are quite limited in the kinds of experimental questions we can pose in the human (Zola-Morgan and Squire, 1985). We have begun to address this question with an ongoing clinical trial of the effects of nimodipine on eyeblink conditioning as well as other cognitive tasks using normal young and aging human subjects. We are using the same 500 msec trace eyeblink conditioning task with the same computerized behavioral training and analysis routines for human training that we use with rabbits. At this point, we have documented that there is a remarkably similar learning deficit in the trace eyeblink conditioning task in aging humans as in aging rabbits (Figure 3; Disterhoft et al., 1991). These data confirm those reported by other laboratories, although our training parameters were slightly different than those used in the previous studies (Finkbiner and Woodruff-Pak, 1991; Solomon et al., 1991). We do not know what the effect of nimodipine on eyeblink conditioning or other tasks is at this point in our double-blind study. However, there is clearly a precedent for a positive effect on learning and general cognitive function in patients with mild or moderate diffuse organic brain syndrome (Kanowski et al., 1989), in patients with primary degenerative and multi-infarct dementias (Fischhof et al., 1989), and in patients with vascular dementia (Tobares et al., 1989). We are screening both our aging and young subjects on a number of measures so that we will be able to observe nimodipine's effects on relatively normal individuals with a wide range of learning abilities.

We have used our animal model, trace eyeblink conditioning in the rabbit, in an attempt to better understand the cellular mechanisms of the learning deficits which occur as part of the aging process. We have chosen trace conditioning because, in the rabbit at least, this behavioral variant is hippocampally-dependent. One hypothesis concerning the cause of learning and other deficits during aging postulates that altered intracellular calcium levels cause disrupted information transfer in regions such as the hippocampus, which are critical for the learning and memory process (Khachaturian, 1986; Landfield, 1987). As explained in this and the companion chapter (Thompson et al., 1991), we have observed that nimodipine causes marked enhancement of associative learning rates in the aging rabbit. We have also shown with *in vivo* and *in vitro* neurophysiological techniques that nimodipine enhances the excitability of hippocampal CA1 neurons in an age- and dose-dependent fashion. These CA1 hippocampal neurons are especially interesting because they show dramatic excitability increases during eyeblink conditioning in young rabbits and demonstrate characteristic changes during aging which result in reduced excitability and reduced capacity for information processing. Thus, we are currently attempting a direct test of our hypothesis that nimodipine enhances learning rate, specifically in eyeblink

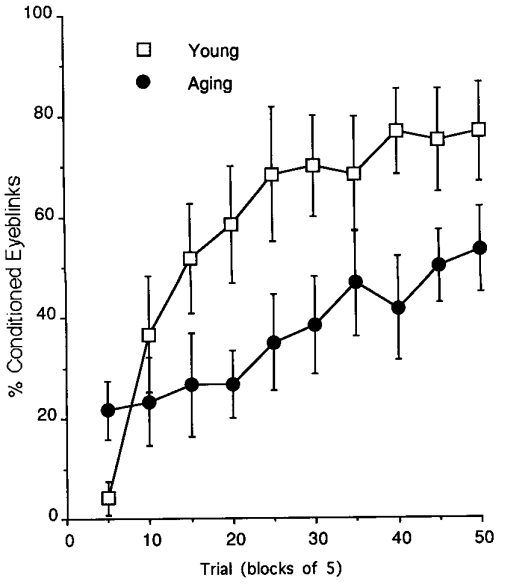

Figure 3. Acquisition curves for trace eyeblink conditioning in a group of young (mean age, 24.9 yr) and aging (mean age, 66.8 yr) human subjects. There were 12 subjects in each group. The young subjects learned the eyeblink conditioning task significantly better than the aging subjects ($p < .04$). The training parameters were the same as those used in the Deyo et al. (1989a) study in which intravenous nimodipine was administered to aging and young rabbits.

conditioning, in aging humans whose hippocampi are likely to be less excitable than those in younger humans.

Our goal is to use insights gained from our preclinical research to define compounds which may be used clinically to help ameliorate aging-related deficits in cognition and especially learning. We are well aware of the pitfalls of attempting to generalize from animal models to the human. But we feel that our multi-level analyses, comparing data from several preparations within one species as well as from one learning task across species, is of great utility and has good face validity. The approach we are using to evaluate nimodipine may also be used with other compounds. It should allow us to make progress, for example, toward defining how nootropic drugs work in the aging brain. Understanding mechanism of action is a major positive step toward the design of compounds which are more effective in dealing with learning deficits seen in "normal" aging and in Alzheimer's disease.

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