pattern: stretch acts on the between-bursts closed time, without substantially altering either open times or brief closed times. In stretch-sensitive channels, therefore, slow mechanical transduction processes and fast kinetic processes may represent modes of gating arising from spatially distinct regions of the channel.

Several additional observations on SI channels are worth noting. The maximum number of SI channels in any patch was ten and the minimum in patches that exhibited SI events was two, a range corresponding to that for SA channels in *Lymnaea* neurons. (Density per patch is obtained from the maximum number of stretch-sensitive elementary amplitudes, as seen in Fig. 2B). SI channels, like SA channels, showed no obvious voltage dependence; spontaneous SI channel activity at V_{rest} was evident with K^+, Tl^+, or Rb^+ in the pipette and no inactivation occurred with depolarization. Normal-looking SI events were observed with both 10 m*M* tetraethylammonium and 1 m*M* quinidine (for example, Fig. 1A) in the pipette. The phenomenon of channel inactivation by stretch is not unique to this preparation; SI channels have been observed in mammalian astrocytes (*16*).

A number of properties shared by the two stretch-sensitive channels (the parallel kinetic effects of stretch on a between-bursts closed state in both, the similarities in membrane densities, the concurrent changes of SI and SA activity in a given patch) are consistent with the possibility that the channels are linked to a common transduction mechanism. A good candidate is the submembranous filament network proposed by Sachs (*3*). The discovery of an SI channel in parallel with the SA channel also raises the interesting prospect that yet other integral membrane proteins—ones implicated in cell motility, cell compliance, or osmoregulation, but with "outputs" that are not necessarily measurable with a patch clamp (carriers, enzymes)—might also be influenced by membrane tension.

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7. SI channels were observed in 13 out of 219 patches made on cell bodies with pipettes made from small bore (outside diameter, 1.65 mm; inside diameter, 0.85 mm) tubing. When such pipettes were used on growth cones, SI channel activity was not observed (15 patches), but with wider bore pipettes (outside diameter, 1.65 mm; inside diameter, 1.15 mm), 3 of 11 successfully patched growth cones exhibited SI channels. This frequency of occurrence represents a minimum; it is likely that patches were discarded as being merely "noisy" when in fact they were displaying multiple spontaneously active SI channels. On two cells in which SI channels were noted, second and third patches were obtained. All showed SI and SA currents, indicative, for these cells at least, of a homogeneous channel distribution.
8. SA channel activity was recognized by the outwardly rectifying current-voltage relations [normal saline (NS) in the pipette, cell-attached], by conductance (~30 to 40 pS under these conditions), and by kinetics (brief bursts activated by stretch).
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20. We thank J. A. Connor and M. D. Schneider for their helpful comments on the manuscript. Supported by the Natural Sciences and Engineering Research Council of Canada and the Muscular Dystrophy Association of Canada.

1 September 1988, accepted 23 November 1988

Nimodipine Facilitates Associative Learning in Aging Rabbits

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Nimodipine is one of several dihydropyridines that block calcium channels. Originally administered to improve cerebral blood flow in elderly patients with chronic cerebrovascular disorders, nimodipine was noted to facilitate learning. These observations led to the present investigation of the effects of nimodipine on associative learning in aging rabbits. Nimodipine accelerated acquisition of conditioned eye-blink in both young and aging rabbits without altering the amplitude of responses to the conditioned or unconditioned stimuli or causing nonspecific responding. Thus, nimodipine may be a candidate for an effective treatment for age-related learning deficits.

ONE OF THE MOST DEBILITATING consequences of aging can be memory loss. Although many changes occur within the central nervous system during aging (that is, decreases in neurotransmitter synthesis and degradation, decreases in receptor number, and increases in cell loss), the perturbation of normal Ca^{2+} metabolism appears to be an important factor correlated with both the age-related physiological deficits and the learning and memory deficits (*1, 2*).

There is a relation between Ca^{2+} metabolism and selected mechanisms of learning and memory in aged subjects. (i) A Ca^{2+}-activated K^+ current is reduced in hippocampal neurons after associative learning in rabbits (*3*). This same current is prolonged in hippocampal neurons from aging brain and may contribute to the learning deficits that often accompany normal aging (*4*). (ii) The elevation of plasma Mg^{2+} (a competitive inhibitor of many actions of Ca^{2+}) improves reversal learning in both aged and young rats (*5*). (iii) Alterations in normal Ca^{2+} homeostasis in aged subjects, such as an increase in the intraneuronal Ca^{2+} concentration, can also be toxic to neurons (*2, 6*). Hence, Ca^{2+} channel antagonists would be expected to improve learning and memory in aged subjects by decreasing neuronal influx of Ca^{2+}, thereby reducing prolonged Ca^{2+}-activated currents or minimizing Ca^{2+} toxicity in neurons from aged brain. Nimodipine, a potent Ca^{2+} channel blocker (*7*), has been noted to enhance learning and memory in older persons with chronic cerebrovascular disorders (*8*).

Here we have tested the effect of nimodipine on eye-blink conditioning of rabbits. This well-studied behavioral system is useful, because both aged humans and rabbits show similar deficits in the acquisition of this conditioned response (*9, 10*).

Thirty-six experimentally naïve New Zealand albino rabbits (*Oryctolagus cuniculus*) were assigned to one of four treatment groups based on age and drug treatment

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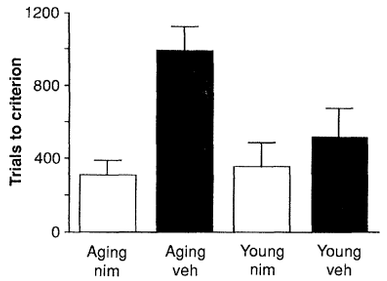

Fig. 1. Summary of the mean number of trials to reach the criterion of eight CRs in any block of ten trials in each of the trace-conditioned treatment groups. Error bars indicate SEM ($n = 6$).

(*11*). These groups were young adults (3 months) receiving vehicle infusions, young adults receiving nimodipine (BAY e 9736) (1.0 μg kg^{-1} min^{-1}), aging adults (mean age, 37.1 months) receiving vehicle infusions, and aging adults (mean age, 37.7 months) receiving nimodipine (1.0 μg kg^{-1} min^{-1}).

The apparatus and behavioral training were similar to those described (*12, 13*). All vehicle control animals and half of the nimodipine-treated animals were trained in a trace-conditioning paradigm in which the conditioned stimulus (CS) was an 85-dB, 6-kHz tone of 100-ms duration followed by a 500-ms trace period during which neither the CS nor unconditioned stimulus (UCS) was presented. The trace period was followed by a 150-ms, 2.5-psi corneal air puff (UCS) sufficient to cause a reliable eye-blink response. An unconditioned response (UCR) was the eye-blink occurring in response to the UCS. A conditioned response (CR) was any response occurring after the CS onset but before the UCS onset. Animals received 80 trials per day until performance reached a criterion of eight CRs in any block of ten trials. Training was discontinued after 15 training sessions if the behavioral criterion had not been reached. In order to differentiate nimodipine effects on learning from nonassociative performance enhancement, half of the nimodipine-treated rabbits were pseudoconditioned. Pseudoconditioned rabbits received 160 trials per day of equal numbers of unpaired presentations of the CS and UCS.

A summary of the mean number of trials to reach the criterion of eight CRs in any block of ten trials is presented in Fig. 1. Trace-conditioned aging animals receiving nimodipine reached the performance criterion significantly faster than vehicle controls. Aging vehicle animals clearly demonstrated difficulty in learning the task when compared to young vehicle animals. Aging nimodipine animals not only improved relative to aging vehicle animals but also acquired the task at an acquisition rate similar to that of young animals. CR and UCR amplitudes for the first five training sessions were evaluated for the possible effects of nimodipine on stimulus sensitivity. No significant drug effects were detected on the average amplitude of CRs, indicating that nimodipine increases the number of CRs but has no statistically significant effect on the size of those CRs. The fact that average UCR amplitude was not changed to a statistically significant extent [$F(1,20) = 3.82$, not significant] is consistent with the hypothesis that the nimodipine effect on learning was not due to increased behavioral responsivity to the corneal air puff.

Learning curves constructed for the first five training sessions for all groups (Fig. 2A) indicated that the trace-conditioned aging nimodipine animals began to demonstrate improved performance on the first day of training and continued to learn at an accelerated rate relative to the corresponding control animals [$F(1,20) = 5.218$, $P < 0.05$]. Aging vehicle animals never showed an acquisition level comparable to the nimodipine-treated animals. Indeed, only two of six aging vehicle animals learned the task within 15 training sessions. All aging nimodipine animals learned the task in less than 8 days of training.

An analysis of the learning curves for pseudoconditioned and trace-conditioned nimodipine-treated rabbits was completed to distinguish nimodipine effects on learning from nonspecific effects on performance (Fig. 2B). Trace-conditioned nimodipine-treated rabbits demonstrated more CRs than pseudoconditioned animals, which gave no evidence of learning. That nimodipine increased responses to the CS only when it was paired with the UCS indicates that nimodipine causes facilitation of associative learning rather than a nonspecific increase in spontaneous blinking or in sensitivity to the CS.

Our observation that young vehicle rabbits acquired the conditioned eye-blink response faster than aging vehicle animals is consistent with earlier reports of associative learning deficits in aged subjects (*9, 10*). These data further support the hypothesis that the conditioned eye-blink response in rabbits would be an appropriate model with which to study age-related changes in learning as well as a method for screening potential drugs for the treatment of age-associated learning disorders. Eye-blink conditioning is particularly appealing since the same task used in an animal model may also be used with few or no changes to study associative learning in human subjects (*13*).

Many nootropics that are effective in improving learning in aging animals and humans are cerebrovasodilatators (*14*). It is possible that the facilitation of learning by means of nimodipine was due to an enhancement of cerebral blood flow by inhibiting Ca^{2+} channels in vascular smooth muscle. Alternatively, our data are consistent with evidence that has outlined the importance of Ca^{2+} metabolism in age-related dementia: (i) Neuronal Ca^{2+} homeostasis is altered during aging, resulting in toxic endogenous Ca^{2+} levels (*2, 6*). (ii) Nimodi-

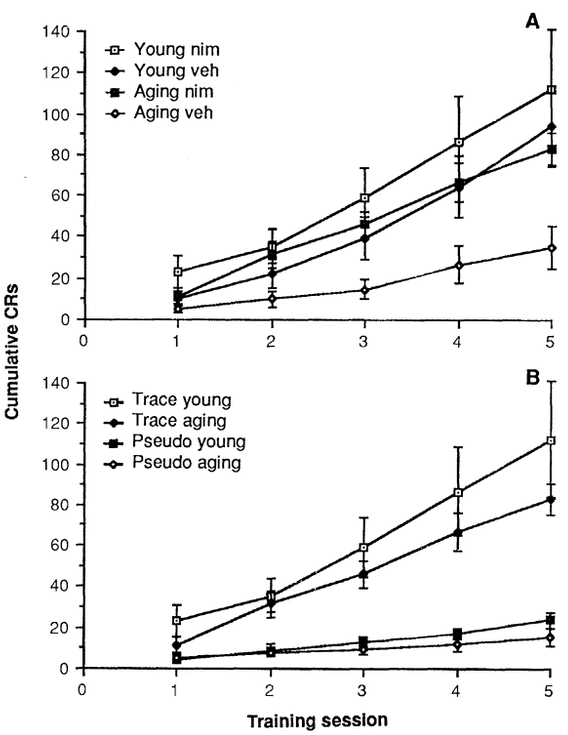

Fig. 2. (**A**) Cumulative CRs are presented for each trace-conditioned treatment group for each of the first five training sessions. (**B**) Cumulative CRs are presented for trace and pseudoconditioned nimodipine-treated animals. In (A) and (B), error bars indicate SEM ($n = 6$).

pine blocks Ca^{2+} currents in hippocampal neurons (*7*). Calcium concentration is a critical factor mediating K^+ currents that are decreased in hippocampal neurons from young animals conditioned to make the eyeblink response (*3*). (iii) Calcium-activated enzymes (Ca^{2+}-activated neutral protease and protein kinase C) have been implicated in regulating specific intracellular mechanisms correlated with learning and memory in young animals (*15*). These enzymes would not be expected to function optimally in aging brain in which endogenous intracellular Ca^{2+} levels are abnormal. These findings together with our present data suggest that Ca^{2+} antagonists such as nimodipine could ameliorate learning deficits in aging animals.

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16. Supported by a gift from the Pharmaceutical Division of Miles Inc., a grant from the American Federation on Aging Research, and NIH grant 1 RO1 NS23482. We thank J. P. Black, M. de Jonge, R. A. Janis, A. J. Krutsch, and J. R. Moyer for comments during this project.

19 August 1988; accepted 6 December 1988

Overexpression of Transforming Growth Factor α in Psoriatic Epidermis

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Transforming growth factor α (TGF-α) is produced by and required for the growth of epithelial cells and is angiogenic in vivo. Since epidermal hyperplasia and angiogenesis are hallmarks of psoriasis, TGF-α gene expression was analyzed in epidermal biopsies of normal and psoriatic skin. TGF-α messenger RNA and protein are much more abundant in lesional psoriatic epidermis than in normal-appearing skin of psoriatic patients or in normal epidermis. In contrast, messenger RNA levels of transforming growth factor β1 (TGF-β1), which inhibits epithelial cell growth, are not significantly different in normal, uninvolved, and lesional psoriatic epidermis. Thus, psoriatic epidermal hyperplasia may involve increased expression of a keratinocyte mitogen (TGF-α) rather than deficient expression of a growth inhibitor (TGF-β1).

PSORIASIS IS A COMMON SKIN DISease in which epidermal hyperproliferation is prominent (*1*). Other characteristic features of psoriasis include capillary elongation and dilatation and the presence of acute and chronic inflammatory cells of the dermis and epidermis (*2*). The recurrent and fluctuating nature of psoriasis is consistent with abnormally unstable regulation of a nonmalignant pattern of epidermal growth, vascular alterations, and dermal inflammation normally observed in the healing of wounded skin (*3*). Identification of factors capable of coordinately directing these responses, their cellular sources, and their cellular and molecular targets could provide important clues into the pathogenesis of psoriasis and other hyperplastic skin diseases and the process of wound healing.

TGF-α is a candidate for direct regulation of the epidermal and angiogenic components of the inflammatory hyperplastic response in psoriasis. TGF-α is structurally related to epidermal growth factor (EGF) and interacts with the same receptor as EGF (*4*). Both molecules are potent positive regulators of epithelial cell growth (*5, 6*), but TGF-α appears to be more potent than EGF in inducing mitosis and migration of human skin keratinocytes (*6*). Since human skin and cultured normal human keratinocytes produce TGF-α (*5*), its overexpression in keratinocytes could be responsible for the initiation or the maintenance of epidermal hyperproliferation in a psoriatic lesion. TGF-α has angiogenic activity in vivo surpassing that of EGF (*7*). Since the dermoepidermal junction is permeable to molecules the size of TGF-α (*8*), the marked dermal angiogenic response characteristic of psoriasis could be mediated by overproduction of TGF-α by keratinocytes. This would be consistent with the observation that the epidermis is much more potent than the dermis as a source of angiogenic activity (*9*).

We evaluated the expression of TGF-α at the levels of steady-state mRNA and protein in normal epidermis and in the normal-appearing (uninvolved) epidermis and lesional epidermis of patients with psoriasis. Since TGF-β gene expression occurs in human keratinocytes (*10*) and in phorbol ester–treated mouse skin (*11*), and since TGF-β can antagonize the growth-promoting effects of EGF and TGF-α in human and murine keratinocytes (*10*), we also assayed the expression of the TGF-β1 gene in normal and psoriatic skin.

Samples of epidermal tissue were obtained by keratome biopsy (*12*) from normal

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