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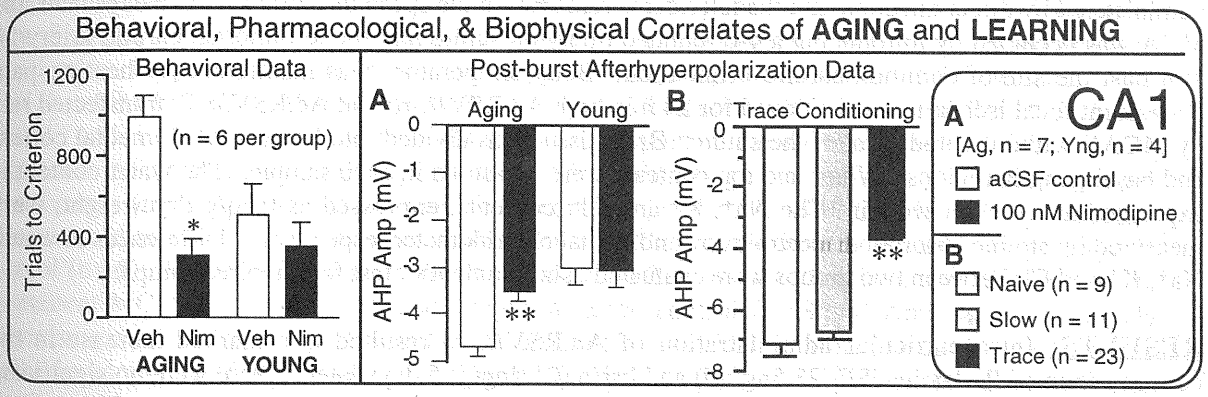
XI-3. CALCIUM HYPOTHESIS OF NEURONAL PROTECTION BY CALCIUM ANTAGONISTS—ENHANCEMENT OF EYEBLINK CONDITIONING IN AGING

J. F. Disterhoft, Jr., J. R. Moyer, L. T. Thompson and M. C. Carrillo *(Cell and Molecular Biology, Northwestern University Medical School, Chicago, IL 60611, U.S.A.)*

Associative learning is accompanied by a number of changes in the brain, many mediated by calcium. We have used eyeblink conditioning, a well controlled learning task in animals and humans, to elucidate them. Our studies have focused on the hippocampus, a temporal lobe structure known to be important for storage of new information during learning in mammalian brain (1). Hippocampal neurons show enhanced firing rates during learning correlated with behavioral acquisition; they also show a reduction of both a calcium-mediated afterhyperpolarization (AHP) and of spike frequency adaptation (accom), likely mechanisms for their enhanced activity during learning. Aging animals and humans show deficits in eyeblink conditioning (EBC). Aging hippocampal neurons show increased AHPs, accomodation and altered calcium buffering, which contribute to the age-related learning deficits. Excitability changes, i.e., reductions in the AHP and in accomodation, only occur in aging rabbits that learn the EBC task (trace), not in animals that are trained but do not acquire the task (slow). Intravenous nimodipine (nim), a dihydropyridine calcium channel antagonist, caused aging rabbits to learn the EBC task as quickly as young controls (veh), showed a dose-dependence and was effective orally in both humans and rabbits.



We have done a series of *in vivo* and *in vitro* cellular physiological studies to determine how nimodipine may increase learning rate. Nimodipine strongly enhanced the firing rate of single hippocampal pyramidal neurons while suppressing the activity of interneurons recorded *in vivo* in an aging-dependent fashion; maximal effect was seen at the behaviorally most effective dose. The AHP was markedly larger in aging rabbit CA1. Nimodipine reduced the post-burst AHP, accomodation and the calcium action potential in an age- and concentration-dependent fashion (2). These data suggest that nimodipine directly alters membrane conductances of neurons known to be involved in eyeblink conditioning to improve learning in aging brain. Nimodipine presumably reduces the age-related functional changes in these neurons.

A recently completed double-blind clinical trial showed that nimodipine enhanced eyeblink conditioning levels in normal aging subjects when given orally over a three month period. This effect was very marked in those aging subjects who demonstrated low levels of eyeblink conditioning before drug administration was begun. No effect was seen in the aging subjects who performed well at baseline or in young subjects. The clinical implications of our work lie in the attempt to counteract learning deficits in aging humans, especially those who are learning-impaired, and/or those with Alzheimer's disease (3).

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