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CHOLINERGIC FACILITATION OF TRACE EYEBLINK CONDITIONING IN AGING RABBITS

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Summary

The hippocampus is importantly involved in learning and memory, and is severely impacted by aging. In *in vitro* hippocampal slices, both the post-burst afterhyperpolarization (AHP) and spike-frequency accommodation are reduced in hippocampal pyramidal neurons after hippocampally-dependent trace eyeblink conditioning, indications of increased cellular excitability. The AHP results from the activation of outward potassium currents, including sI_{AHP} and muscarine-sensitive I_M. The AHP is significantly increased in aging hippocampal neurons, potentially contributing to age-associated learning deficits. Compounds which reduce the AHP and spike-frequency accommodation could facilitate learning in normal aging or in age-associated dementias such as Alzheimer's disease. The cholinesterase inhibitor metrifonate enhances trace eyeblink conditioning by aging rabbits and reduces the AHP and accommodation in hippocampal CA1 neurons in a dose-dependent manner. These reductions are mediated by muscarinic cholinergic transmission as they are blocked by atropine. Hippocampal neurons from metrifonate treated but behaviorally naive rabbits were more excitable and not desensitized to the effects of metrifonate since the AHP and accommodation were further reduced when metrifonate was bath applied to the neurons. These observations suggest that the facilitating effect of chronic metrifonate on acquisition of hippocampally dependent tasks is mediated at least partially by increasing the baseline excitability of CA1 pyramidal neurons. The issue of whether learning can be facilitated with muscarinic cholinergic agonists, in addition to cholinesterase inhibitors, was addressed by training aging rabbits during intravenous treatment with the M_1 agonist CI1017. A dose-dependent enhancement of acquisition was observed, with rabbits receiving 1.0 or 5.0 mg/ml CI1017 showing comparably improved learning rates as those receiving 0.5 mg/ml or vehicle. Sympathetic side effects, mainly excess salivation, were seen with the 5.0 mg/ml dose. Post-training evaluations suggested that the effective doses of CI1017 were enhancing responsivity to the tone conditioned stimulus. These studies suggest that muscarinic cholinergic neurotransmission is importantly involved in associative learning; that learning in aging animals may be facilitated by enhancing cholinergic transmission; and that the facilitation may be mediated through actions on hippocampal neurons.

Key Words: acetylcholine, afterhyperpolarization, aging, hippocampus, learning

The hippocampus is a critical neural system in learning which is very much affected by the aging process. Hippocampal lesions in humans and animals cause severe deficits in the ability to transfer information from short- to long-term stores and thus form new memories (1). We have adopted a hippocampally-dependent trace paradigm to analyze hippocampal involvement in learning (2,3). In the trace paradigm a blank "trace" period intervenes between conditioned stimulus (CS) offset and unconditioned stimulus (US) onset, which forces the rabbit to form a very short term memory of the CS in order to successfully predict US onset and perform conditioned responses timed properly to avoid the US. Trace eyeblink conditioning taps the hippocampal system's role in forming temporal associations and therefore this structure is necessary for learning this task (4,5).

Use of a hippocampally-mediated learning task is particularly relevant in studies of aging. Many studies have demonstrated structural (6), neurophysiological (7), and neurochemical (8,9) changes in the aging hippocampus, specifically to cholinergic systems. In addition to eyeblink conditioning, other hippocampally-dependent tasks such as spatial learning in rats (10) are also impaired in aged animals (7,11).

Eyeblink Conditioning : A Behavioral Model for Studying Learning Deficits in Aging

Eyeblink conditioning is used as a "model system" to analyze the neural substrates of learning (12,13,14). Eyeblink conditioning has many advantages for studying the neurobiology of learning deficits in both aged humans and animals (15,16). It is impaired in both older humans and animals (17,18). The changes across the lifespan of rabbits parallel those in humans (19), strengthening its validity as a model system. We have demonstrated that trace eyeblink conditioning is impaired in middle aged (24 mo) rabbits, and severely impaired by 30 mo of age (20). Additionally, aging rabbits are behaviorally heterogeneous, offering a subset of aging rabbits for study which are unable to learn even after extensive training.

Postsynaptic Outward Potassium Currents Regulate Neuronal Excitability in Learning

Both the afterhyperpolarization (AHP) which follows a burst of action potentials and spike frequency accommodation are reduced in CA1 and CA3 pyramidal neurons after hippocampally-dependent trace eyeblink conditioning (21,22). These reductions increase neuronal excitability and are well correlated with behavioral acquisition. Importantly, these excitability increases decay as expected if the hippocampus serves as an intermediate storage buffer in acquisition of new associations. These alterations are localized to the hippocampus after learning, as they occur in *in vitro* slices separated from their normal afferent and efferent connections (23). They are postsynaptic, as they are evoked by intracellular current injection and persist after block of sodium spike-dependent synaptic transmission (24).

An important conceptual issue regarding our experimental program should be addressed. When most neuroscientists think about how information is stored in neural networks during learning, changes located at the synapse are considered first. The description of how "Hebb synapses" might change during a hypothetical learning sequence (25) has inspired much work on model systems such as long term potentiation (26). But it should be pointed out that other mechanisms are available for altering synaptic efficacy, e.g., by modulation of excitability at the postsynaptic level (27). Adjustment of cellular excitability could amplify or attenuate synaptic changes occurring in distal dendrites (28), and affect neuronal firing output after learning. Possible functions of alterations in the afterhyperpolarization would be to control dendritic excitability, modulate neuronal gain or act as a temporal filter of information coming into the dendrites. This is especially relevant when considering cholinergic neurotransmission as involved in learning. Acetylcholine presumably acts as a neuromodulator by its action on slow outward potassium currents (27). Synaptic events, in this view of learning, produce post-synaptic changes with some degree of persistence, or "memory" of the associative event.

We have been quite successful in our efforts to define postsynaptic excitability changes in hippocampal neurons analyzed *in vitro* after eyeblink conditioning. We offer compelling evidence that calcium-mediated outward potassium currents are reduced in a conditioning-

specific fashion to increase hippocampal excitability in learning (20,21,29). Similar reductions in these or other outward potassium currents are well documented in invertebrate and mammalian learning models (30,31,32). The generality of our findings across vertebrate and invertebrate species suggests that postsynaptic modulation of outward potassium currents may be an important conserved mechanism used to mediate neuronal changes after learning (33).

Calcium-Activated Potassium Currents and Calcium Antagonists in Aging and Learning

The relevance of AHP reductions during learning in young adults to learning deficits in aging animals may be rather direct. Landfield and Pitler (34) first demonstrated that the AHP is prolonged in hippocampal CA1 neurons from aged rats. They suggested that this increase was a causative factor in learning impairments in aging. We found that both the AHP and spike frequency accommodation were increased in aging rabbit CA1 neurons, i.e., the neurons were less excitable (35).

One experimental approach of our own and of others used calcium channel blockers to address the hypothesis that an inability to reduce the AHP contributes to the learning deficits in aging animals. For example, elevation of plasma magnesium (a competitive inhibitor of calcium) improved reversal learning in both aged and young rats (36). Because of its ability to cross the blood brain barrier (37), the calcium antagonist nimodipine was tested in a variety of learning and behavioral tasks in aging mammals. Nimodipine markedly facilitated acquisition of the trace eyeblink conditioned response in aging rabbits (38,39,40) and humans (41); improved sensorimotor behaviors in aging rats (42); reversed open field deficits in aging rabbits (43); improved delayed matching-to-sample performance in aging primates (44); and improved spatial learning in aging rats (45,46).

The often dramatic behavioral effects of calcium antagonists in aging animals suggested that research focusing on compounds which reduced efflux through the slow calcium-activated potassium channel (sI_{AHP}) was a fruitful avenue for developing drugs that would facilitate learning in aging and dementia. Such an approach was based on our understanding of important cellular changes in young neurons during learning, and of cellular alterations in aging neurons that affected the learning process. Our observations that calcium channel antagonists increase hippocampal excitability *in vivo* (47) and reduce the AHP and decrease accommodation *in vitro* (35) in aging neurons at the same concentrations which facilitate learning in aging animals were important steps in determining cellular mechanisms of nimodipine's behavioral effects. A similar experimental approach should be fruitful in understanding mechanisms of action of cholinergic modulation of learning in aging brain.

Metrifonate Improves Associative Learning in Aging Rabbits

The hippocampus is a brain region which is importantly involved in mediating learning and memory (1,5) and has been shown to demonstrate alterations that correlate with the deficits in learning which occur during aging (48,49). Of special interest are the alterations that occur in cholinergic neurotransmitter systems that occur during aging and are especially prominent in Alzheimer's disease (8,50). This is the theoretical basis for one approach to the treatment of Alzheimer's disease in which reductions in cholinergic neurotransmission are compensated for by blocking cholinesterases which normally act to temporally limit the activity of acetylcholine. We have demonstrated that the cholinesterase blocker metrifonate improves hippocampally-dependent trace eyeblink conditioning in aging rabbits, a group in which learning is markedly impaired (20). In our first study, we showed that oral administration of metrifonate improved learning at doses of both 12 and 24 mg/kg, while 6 mg/kg was ineffective (51). The 24 mg/kg dose was somewhat less effective than the 12 mg dose, suggesting an inverted U dose/response curve. In addition, we began metrifonate treatment only one week prior to behavioral training but later determined that the asymptotic inhibition of cholinesterase in red blood cells did not occur until the third week of metrifonate treatment. A follow-up study, in which metrifonate pretreatment was begun three weeks prior to behavioral training, compared the effect of 12 and 24 mg/kg of metrifonate given

orally with 100 mM sodium citrate vehicle as a control in three groups of rabbits (52). The behavioral effect was stronger and less variable in the second experiment. Behavioral enhancement was clearly evident in the group learning curves by the fourth training session, had asymptoted after 15 training sessions, and was retained for 4 weeks after metrifonate administration was stopped. However, there was no difference in behavioral effectiveness between the 12 and 24 mg/kg doses in the second study. The metrifonate groups performed approximately twice as many conditioned responses as the control rabbits at the end of training.

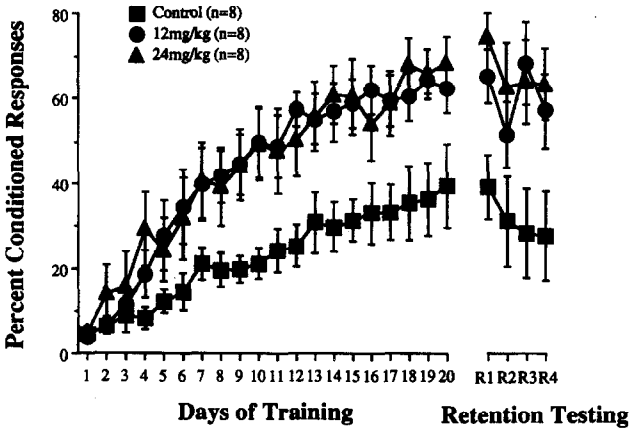

Fig. 1

Metrifonate enhanced acquisition early in training and improved retention of trace eyeblink conditioning for up to four weeks after dosing stopped in aging rabbits (reprinted from 52).

Cholinergic modulation of excitability in hippocampal CA1 neurons

Benardo and Prince (53,54) demonstrated that tonic cholinergic release occurred in the hippocampal slice, as muscarinic antagonists (such as atropine) decreased membrane resistance, via an increase in I_M (a tonic potassium current, sensitive to block by muscarine, that contributes both to the resting membrane potential and to the post-burst AHP). Anticholinesterases such as eserine (55) had opposite effects to atropine, mimicking the effects of bath (exogenous) application of carbachol or other ACh agonists. The net effect of cholinergic agonists was to increase the excitability of CA1 neurons (56). More specifically, exogenous carbachol or muscarine depolarized CA1 pyramidal cells and reduced both the AHP and spike-frequency accommodation (57), while specific nicotinic agonists such as dimethylphenylpiperazinium (DMPP) were without effect. Anticholinesterases strongly enhanced the effects of exogenous muscarinic agonists (57), but also when applied alone (i.e. without exogenous agonists) were still capable of significantly increasing CA1 excitability (58). All effects could typically be washed out in slices, indicating the reversability of receptor- or substrate-specific actions.

Metrifonate Increases Excitability in Young and Aging Hippocampal Neurons

One goal of our studies was to determine dose ranges of metrifonate (*in vitro*) that significantly reduce both the AHP and accommodation. We then compared these effects to those obtained after chronic treatment with metrifonate. Since enhanced excitability has been repeatedly demonstrated after learning by us (21,22,29,59) and others (60), and since CA1 excitability is severely reduced in aging (34,35), a link between these findings and between those with metrifonate should be readily observable. To this end, we examined the effect of metrifonate bath applied onto hippocampal slices from young and aging rabbits or chronically administered orally to aging rabbits before the slices were prepared (61). Metrifonate reduced the

afterhyperpolarization and spike frequency accommodation, i.e., increased neuronal excitability, in hippocampal neurons from both young and aging rabbits in a dose-dependent fashion in doses ranging from 10 - 200 μM. The reductions were mediated by muscarinic cholinergic transmission, as they were blocked by atropine. Aging rabbits chronically treated orally with metrifonate (12 mg/kg for 3 weeks) had significantly reduced spike frequency accommodation as compared to CA1 pyramidal neurons from vehicle-treated animals. Chronic metrifonate treatment did not desensitize the neurons to metrifonate, as bath application of metrifonate caused further reduction in both the AHP and accommodation in CA1 neurons. These data suggest that the facilitating effect of chronic metrifonate treatment on acquisition of trace eyeblink conditioning by aging subjects may be due at least partially to increased excitability of CA1 pyramidal neurons.

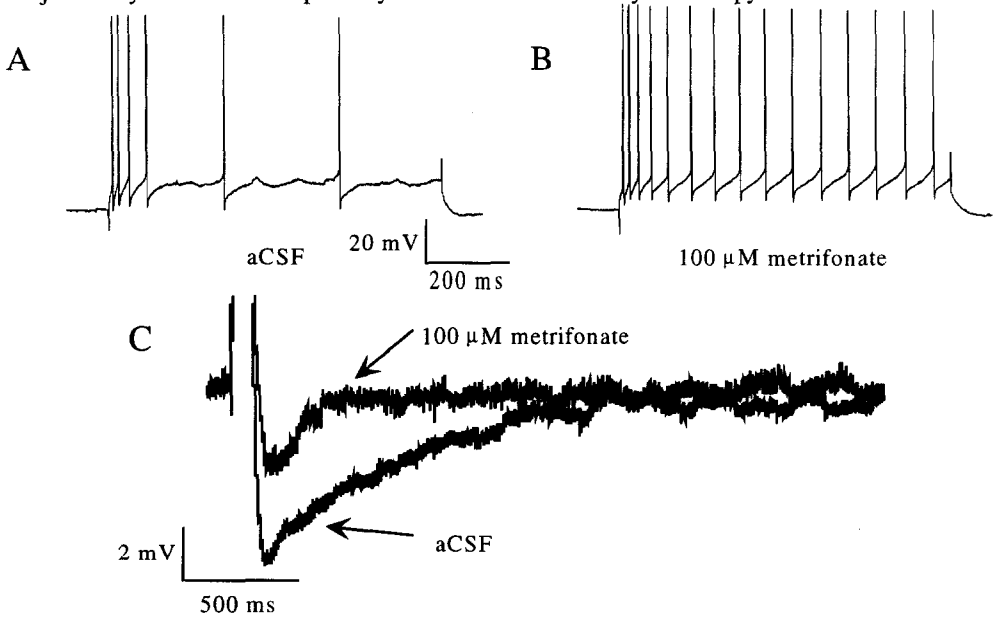

Fig. 2

100 μM metrifonate reduced spike frequency accommodation (A vs B) and the post-burst afterhyperpolarization (C) in CA1 pyramidal neurons from behaviorally naïve, untreated aging rabbits

The M_1 Agonist CI1017 Enhances Trace Eyeblink Conditioning in Aging Rabbits

A cholinesterase inhibitor such as metrifonate theoretically enhances cholinergic function by slowing the breakdown of neurotransmitter which is present at reduced levels in the aging or Alzheimer's disease affected brain. An alternative strategy is to activate muscarinic receptors directly with an agonist. The muscarinic receptor of most interest with respect to learning in aging brain is the M_1 type, which tend to be expressed most prominently in the brain and particularly in the hippocampus (62). The rationale for this approach, of course, is that the use of a selective M_1 agonist should activate the central receptors involved in learning and memory while causing minimal peripheral cholinergic side effects. We have therefore evaluated the effectiveness of CI1017 in hippocampally-dependent trace eyeblink conditioning. This compound has been identified as a relatively M_1-selective partial muscarinic agonist by cell metabolism, cell amplification, and second messenger assays (63), and has been shown to improve spatial learning in rodents and a continuous performance task in primates (64).

Drug delivery to aging (30-36 mo, avg wt 4.5 Kg) rabbits was by means of a chronically implanted subcutaneous venous access port. CI1017 was delivered at 2.7 ml/hr for 30 min before and during the daily trace eyeblink conditioning training sessions. Behavioral training procedures were identical to those used in previous studies, i.e., a 100 msec 6 KHz tone was paired with a

corneal airpuff after a 500 msec trace interval (20,38,51,52). Rabbits were given 80 paired conditioning trials each day. Three drug dose groups (5.0, 1.0, 0.5 mg/ml) plus vehicle were run. There were significantly more CRs seen in the 5.0 and 1.0 mg/ml groups of rabbits as compared to both the 0.5 and 0.0 mg/ml drug groups. The high (5.0 and 1.0) and low (0.5 and 0.0) drug groups were not different from each other, respectively. There were no differences in variables such as peak amplitude or latency of the conditioned response or of unconditioned response size between groups. The other interesting difference observed was that the generalization gradient (evaluated by systematically reducing the tone conditioned stimulus amplitude) was broader for the high drug groups as compared to the low dose groups when evaluated at the end of training during delay conditioning after the final session of trace conditioning. This indicated that the effective drug doses made the rabbits more responsive to the tone conditioned stimulus. Sympathetic side effects, primarily salivation, were prominent in the 5.0 mg/ml drug group. They were essentially nonexistent in the 1.0 mg/ml group, which had comparable behavioral enhancement to the higher dose 5 mg/ml group, and were also not present in the low dose rabbits. These data indicate that the M_1 agonist CI1017 is effective in facilitating learning of a hippocampally mediated associative learning task without causing unwanted peripheral sympathetic side effects. A comparison of the learning curves showed that CI1017 enhanced associative learning in a qualitatively and quantitatively similar fashion as did metrifonate (52).

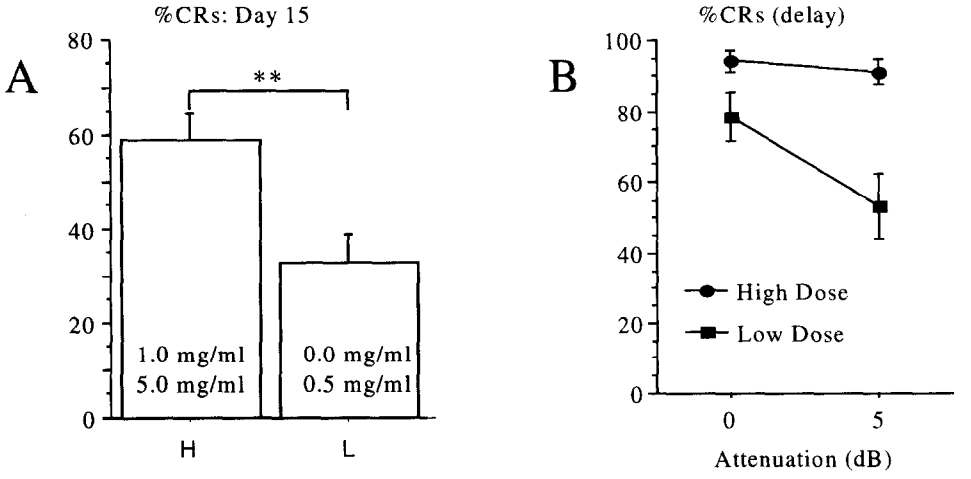

Fig. 3

A. CI1017 enhanced acquisition of trace eyeblink conditioning in aging animals at the 1.0 and 5.0 mg/ml doses. There was no difference in conditioned response probability on Day 1 but a highly significant increase in the higher dose animals on Day 15. **B.** Responsivity to the tone conditioned stimulus was also increased at the higher drug doses.

Comment

We have summarized the results of two separate studies which indicate that enhancing cholinergic neurotransmission with the cholinesterase inhibitor metrifonate is effective in facilitating associative learning in aging animals. This is not especially surprising, as cholinesterase inhibitors have been shown to be behaviorally effective in a variety of animal and human learning models. But the behavioral enhancements we showed are very substantial, have relatively little variability, last for several weeks following cessation of treatment, and occurred with no obvious side effects. This response profile suggests that metrifonate may be a quite useful compound in treating learning deficits associated with aging and/or Alzheimer's disease.

We have begun to address the mechanisms by which metrifonate may be working. Metrifonate enhances CA1 pyramidal neuron excitability in the hippocampus when bath applied to slices and after chronic treatment in a fashion that mimics the manner of administration in a

learning experiment. The reduced afterhyperpolarization and spike frequency accommodation are similar to those learning-specific changes observed in young and aging hippocampal neurons. Hippocampal neuron excitability has been observed to be reduced in aging animals, and suggested as one potential mechanism for aging-associated reductions in learning ability. Metrifonate may be facilitating learning by bringing hippocampal neuron excitability in aging animals into a range more like that of young animals. Our data also support the suggestion that one important index of the effectiveness of compounds in facilitating learning in aging mammals may be their ability to enhance the excitability of hippocampal and/or other temporal lobe system neurons.

Finally, we have demonstrated that the M_1 type muscarinic agonist CI1017 is effective in facilitating the acquisition of a well-controlled hippocampally-dependent associative learning task, trace eyeblink conditioning. In one sense, this is to be anticipated, given the striking learning facilitation we have demonstrated with metrifonate. But the demonstration of learning enhancements with muscarinic agonists has generally been difficult to demonstrate. The fact that we have observed comparable facilitation of learning with a muscarinic agonist as that we observed in the same age rabbits with a cholinesterase inhibitor, in the absence of side effects (for one of the effective doses), is heartening progress. Our pilot data indicates that CI1017 reliably raises CA1 pyramidal neuron excitability in young rabbits as metrifonate does.

Our studies indicate that hippocampally-dependent associative learning can be enhanced in aging rabbits by two different manipulations of the cholinergic system. Since eyeblink conditioning is hippocampally-dependent in the human (65,66) as it is the rabbit (2,3), it will be interesting to determine the effect of manipulations of the cholinergic system on this learning paradigm in the human. The implication of our work is that, if such a facilitation is seen in the human, we have an animal model available in which to fine tune pharmacological parameters to maximize the learning facilitation (dosing regimens, dose levels, age of effectiveness, etc.) and also one in which we can gain a cellular and molecular handle on how the compound(s) are working. This is obviously an important step in the rational design of even better compounds for reversing learning and memory deficits in aging.

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