"BRAIN-SPECIFIC" NUTRIENTS: A Memory Cure?

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Summary—We review the experimental evaluations of several widely marketed nonprescription compounds claimed to be memory enhancers and treatments for age-related memory decline. We generally limit our review to double-blind placebo-controlled studies. The compounds examined are phosphatidylserine (PS), phosphatidylcholine (PC), citicoline, piracetam, vinpocetine, acetyl-L-carnitine (ALC), and antioxidants (particularly vitamin E).

In animals, PS has been shown to attenuate many neuronal effects of aging, and to restore normal memory on a variety of tasks. Preliminary findings with humans, though, are limited. For older adults with probable Alzheimer's disease, a single study failed to demonstrate positive effects of PS on memory performance. For older adults with moderate cognitive impairment, PS has produced consistently modest increases in recall of word lists. Positive effects have not been as consistently reported for other memory tests. There is one report of consistent benefits across a number of memory tests for a subset of normal adults who performed more poorly than their peers at baseline.

The choline compounds PC and citicoline are thought to promote synthesis and transmission of neurotransmitters important to memory. PC has not proven effective for improving memory in patients with probable Alzheimer's disease. The issue remains open for older adults without serious degenerative neural disease. Research on citicoline is practically nonexistent, but one study reported a robust improvement in story recall for a small sample of normally aging older adults who scored lower than their peers in baseline testing.

Animal studies suggest that piracetam may improve neuronal efficiency, facilitate activity in neurotransmitter systems, and combat the age-related decrease in receptors on the neuronal membrane. However, for patients with probable Alzheimer's disease, as well as for adults with age-associated memory impairment, there is no clear-cut support for a mnemonic benefit of piracetam.

Vinpocetine increases blood circulation and metabolism in the brain. Animal studies have shown that vinpocetine can reduce the loss of neurons due to decreased blood flow. In three studies of older adults with memory problems associated with poor brain circulation or dementia-related disease, vinpocetine produced significantly more improvement than a placebo in performance on global cognitive tests reflecting attention, concentration, and memory. Effects on episodic memory per se have been tested minimally, if at all.

ALC participates in cellular energy production, a process especially important in neurons, and in removal of toxic accumulation of fatty acids. Animal studies show that ALC reverses the age-related decline in the number of neuron membrane receptors. Studies of patients with probable Alzheimer's disease have reported nominal advantages over a range of memory tests for ALC-treated patients relative to placebo groups. Significant differences have been reported rarely, however. Whether ALC would have mnemonic benefits for aging adults without brain disease is untested as far as we know.

Antioxidants help neutralize tissue-damaging free radicals, which become more prevalent as organisms age. It is hypothesized that increasing antioxidant levels in the organism might retard or reverse the damaging effects of free radicals on neurons. Thus far, however, studies have found that vitamin E does not significantly slow down memory decline for Alzheimer's patients and does not produce significant memory benefits among early Parkinson's patients. Neither did a combination of vitamins E and C significantly improve college students' performance on several cognitive tasks.

In sum, for most of the "brain-specific" nutrients we review, some mildly suggestive effects have been found in preliminary controlled studies using standard psychometric memory assessments or more general tests designed to reveal cognitive impairment. We suggest that future evaluations of the possible memory benefits of these supplements might fruitfully focus on memory processes rather than on memory tests per se.

Memory decline with age has been well documented in the experimental literature for some time (see A.D. Smith & Earles, 1996). As Figure 1 shows, in humans this decline may start as early as 30 years of age, with significant decline evidenced by middle age, at least for paired-associate memory. These experimental findings are echoed in people's personal observations that as they age, their memory seems to get worse. In a sample of 280 people of varying ages whom we queried, we found a threefold increase from the decade of the 30s to the decade of the 40s in the percentage of people reporting that they

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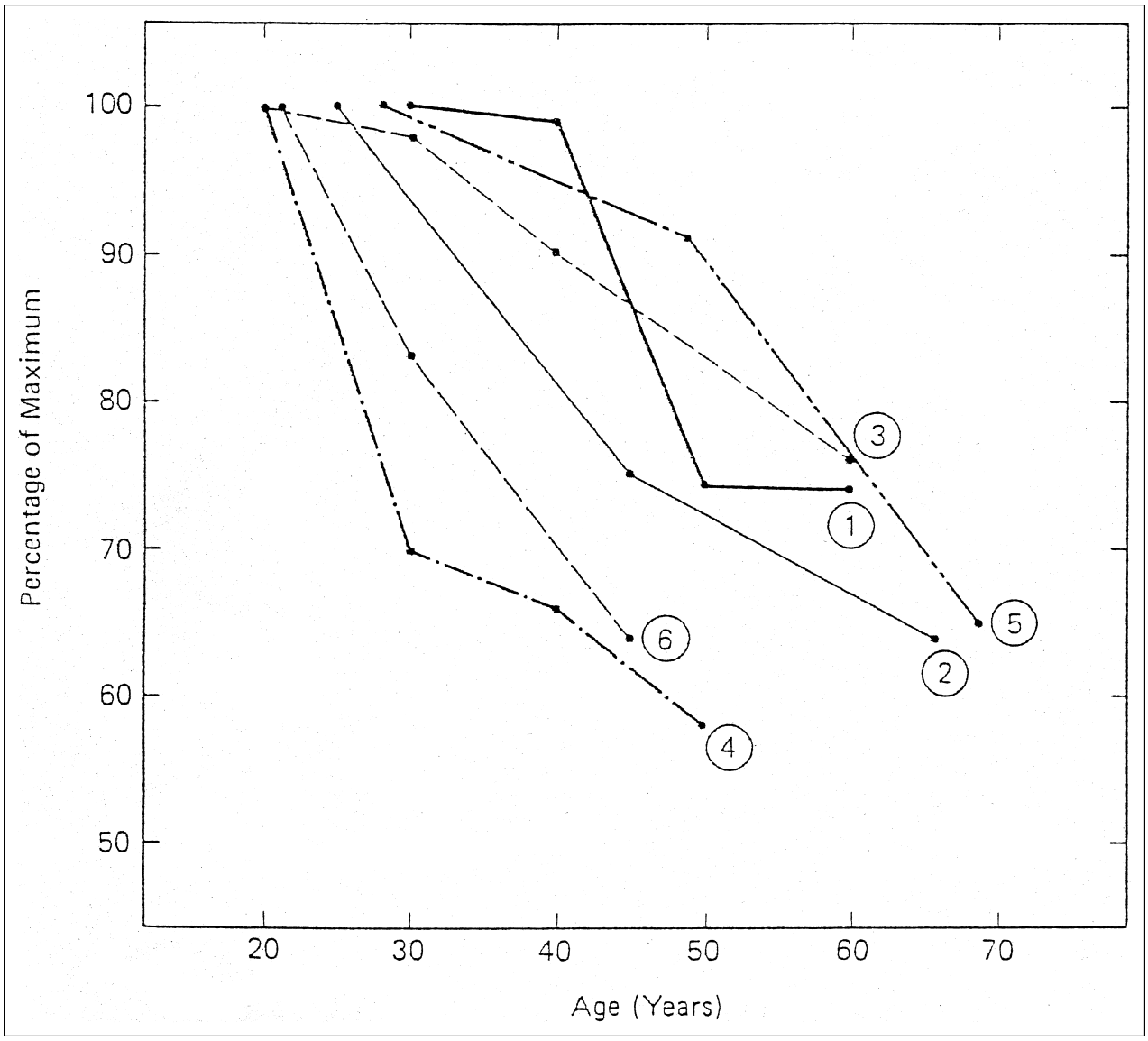

Fig. 1. Paired-associate learning at various ages. The scores are expressed as a percentage of the maximum score across all ages. Each line shows the results of a separate experiment (identified by the number next to the line). Reprinted from Salthouse (1982, p. 126) by permission of the author.

perceived having some problems with memory. Almost a third of the people in their 40s felt that these problems might be suggestive of Alzheimer's disease (Einstein & McDaniel, in press)! Thus, as people age, they appear to have a strong tendency to develop the impression that their memory is declining, an impression that dovetails with the experimental literature.

In view of these observations, it is natural that the public has an interest in supplements that are touted to improve memory, forestall memory decline, or help remedy age-related declines in memory. These supplements are easily available and are widespread, dispensed either individually or in combinations as "memory cocktails." These products are frequently advertised on the radio, in magazines directed at the aging population, and in publications about natural remedies to physical and psychological ailments. It is not surprising, then, that when memory psychologists are engaged in social conversations about memory, they are often asked, "Are there supplements I can take that are supposed to help memory?" and "Do these supplements really work?" These questions are reasonable, and the answers hold importance for individuals who are experiencing age-related memory declines or age-related neural pathology, or who have friends and relatives with such concerns.

Unfortunately, these questions cannot be answered by appealing to the mainstream experimental psychology journals, as the issue has not penetrated these journals. Neither can the questions be answered confidently by examining trade books on "brain fitness," "memory cures," and so on. In the case of such non-peer-reviewed publications, the cautious reader has reason to question the nature of the database examined, the extent to which the scientific database has been probed, and the leniency with which the data have been interpreted. Further, marketing these products as "memory enhancers" and "brain boosters," without any proof of efficacy, is legal as long as there are no claims that they are effective in treating or curing disease or illness.

Accordingly, the purpose of this review is to identify supplements that have enjoyed reputations as memory enhancers, to consider the possible neurological or physiological mechanisms by which they might affect memory, and to report on the existing behavioral evaluations of their efficacy. At the outset, we were unsure whether such scientific studies existed, and were somewhat skeptical that the claims in the popular press about the memory benefits of these supplements would find any support in well-conducted research. To foreshadow our conclusions, we were somewhat surprised by the number of supplements (in addition to ginkgo) that are hypothesized to increase memory functioning and also by the research findings, which do not justify outright dismissal of some of these supplements.

NOOTROPICS, THE AGING BRAIN, AND NEURAL BASES OF LEARNING AND MEMORY

The term *nootropics* (from the Greek "noos" and "tropein," meaning "mind" and "toward," respectively) was originally coined to describe the pharmacology of a particular drug, piracetam (Nicholson, 1990) and has now been adopted more generally as a label for the class of agents that (a) improve cognitive functions like memory and learning; (b) provide neuroprotective effects from various insults; (c) do not possess properties of classical excitants, tranquilizers, and antipsychotics; and (d) have very limited or no side effects (Gabryel & Trzeciak, 1994). In this article, we review the existing experimental evaluations of several widely marketed nonprescription agents claimed to have nootropic effects. These drugs (mostly nonprescription) and nutrients are featured in the popular press as memory- or cognitive-enhancing supplements, and are recommended as part of treatment regimens at some aging clinics. They include *Ginkgo biloba*, phosphatidylserine (PS), vinpocetine, acetyl-L-carnitine (ALC), piracetam, choline-related nutrients thought to be involved in producing acetylcholine (ACh), and antioxidant agents like vitamin E. These are often combined into memory-cocktail supplements and sold commercially. For example, the first four nutrients listed have recently been combined into a single cocktail supplement and sold as Memory 2000 (produced by Natural Balance).

The Aging Brain

The presumed neural benefits of these nootropic agents may articulate well with the neural declines associated with normal aging and with degenerative neural pathologies commonly seen in older adults. The growing evidence suggests at least three prominent global changes in the brain that occur with age. First, the neurons show multiple changes, and neuronal changes are a more decisive hallmark of age than widespread death of neurons (Raz, 2000). Briefly, the aging-related neuronal changes include accumulation of nonessential substances (e.g., yellowish brown lipid lipofuscin—"wear and tear" pigment), loss of essential myelin (fatty material around axons; the axon conducts an electrical signal away from the neuron body, and myelin promotes speedy and reliable propagation of the signal), and general shrinkage. With regard to age-related changes in memory and cognitive functioning, it is perhaps significant that lipid lipofuscin accumulates prominently in cortical neurons (see Raz), and myelin loss is most notable in the association and limbic cortices (specific areas of the cerebral cortex; Kemper, 1994).

Second, the connections between neurons, not just the neurons themselves, change with age. There is a reduction in the branching of dendrites (fibers on which axons of other neurons terminate) and a decline in the number of properly functioning connections between neurons (see Raz, 2000, for a review). Aging may depress the availability of neurotransmitters such as ACh, and ACh seems to be heavily involved in neuron networks associated with memory. Third, with age the cerebrovascular system shows numerous structural changes, diminishing cerebral blood flow, and declining cerebral blood volume. With extreme shortage or suppression of blood flow, a condition called ischemia exists.

As we discuss in the individual sections dedicated to the various nootropic agents, and as we summarize in Table 1, some nootropics may help stem age-related changes in neurons by providing the essential substances for cell membrane health (e.g., PS, citicoline) or by protecting neurons against toxic effects produced by oxidative processes (e.g., antioxidants) and other sources (e.g., ALC, piracetam). Some nootropics may augment neuronal connections by promoting branching of dendritic spines (PS), maintaining neuron receptors (PS, ALC, piracetam), or stimulating the production or release of ACh (cholines, ALC, piracetam). Other agents may function by increasing blood flow (vinpocetine).

The Neural Basis of Learning and Memory

Before proceeding, it is necessary to preview how neuronal functions and connections underlie learning and memory. Because learning and memory involve the retention of information over long periods of time, they must be mediated by relatively permanent changes in the networks of neurons that represent the information. Unraveling the mystery of how this occurs has been a fascinating success story of modern science,

and the broad outline is as follows. It all begins with the release of a neurotransmitter, the chemical messenger between neurons, from terminals in the axon of a neuron. The neurotransmitter molecules then bind to receptors on the membrane of the dendrites of nearby neurons, thereby initiating a complex cascade of events within those neurons that lead to the permanent changes that are memory.

The binding of a neurotransmitter to one type of receptor (ionotropic receptors) allows ions of various kinds to rapidly cross the cell membrane into the neuron. This passage of ions changes the electrical potential between the inside and outside of the neuron and causes the neuron to "fire" an electrical signal. However, this occurs within milliseconds and does not produce a long-term change in the neuron, and thus cannot be the basis of memory.

But there is a second type of receptor. The binding of a neurotransmitter to this type of receptor (metabotropic receptors) induces the production of what are called second-messenger molecules (the neurotransmitter is the first messenger) within the neuron. These second messengers travel within the neuron, initiating a large number of different biological reactions and controlling the functioning of the neuron. The reaction of most importance for memory is the activation of a number of different enzymes called kinases. The functioning of any cell is determined by the proteins that are produced in the cell and their activity, and kinases selectively alter the activity of proteins. Kinases can remain active for hours once activated, and so have time to produce many prolonged alterations within the neuron. In addition, some kinases can enter the nucleus and initiate the activation of specific genes, thereby leading to the production of novel proteins and thus an altered neuron—a memory. Some of these new proteins then produce physical growth of the neural fibers that directly interact with other neurons. For example, new spines may form on the dendrites of the neuron, thus strengthening its connection to the neuron that began it all by releasing the neurotransmitter. These new physical structures can be relatively permanent and form the physical basis for a stable memory. Figure 2 provides an illustrative schematic of the neural processes just discussed.

The compromised communication between neurons that is associated with aging and brain disease may be due to a decrease in the production of neurotransmitters or a deficit in any of the processes involved in the complex cascade of biological events that intervene between the binding of a neurotransmitter to a receptor and long-term alterations in the functional state of the neuron. More specifically, there are likely declines in aspects of the processes within the neuron, such as the activity of kinases, that lead to the long-term, stable changes that form the basis of memory. The theory is that memory decline might be avoided by using nootropic-like agents to slow down neuron and brain-tissue loss and loss of function so as to restore depleted memory-related neural processes.

Because the mnemonic effects of these agents seem most likely to emerge in older populations that are at risk for neural impairment, and because the need for nootropic agents is pressing for aging individuals, especially those with dementias, the scientific evaluation of such agents has been almost exclusively conducted with older adults having demonstrated memory impairment. Ideally, a complete understanding and evaluation of the effects of supplements on memory would specify the particular neural or metabolic influence of each supplement; identify age-related changes in neural functioning; delineate the possible effects of age and supplements on particular neuropsychological systems; and link these effects to particular kinds of memory functioning. Unfortunately, none of these issues is well understood, and the experimental human studies have not been guided by this kind of rich theoretical orientation. In our review of the experimental findings, we have attempted to synthesize as much information pertaining to these fundamental issues as the literature allows, and we hope that in so doing we have provided a solid foundation for further systematic research on nootropic supplements.

We generally limit our review to double-blind, placebo-controlled studies, as placebo and expectation effects can seriously compromise the interpretation of studies without these experimental safeguards (e.g., Greenwald, Spangenberg, Pratkanis, & Eskenazi, 1991). Also, because the companion report by Gold, Cahill, and Wenk in this issue focuses on *Ginkgo biloba*, we limit discussion of ginkgo to one recent experimental finding. Our primary goal is to examine the various other sup-

Table 1. *Theoretical mechanisms of nutrients claimed to be memory enhancers*

Phosphatidylserine
Maintain neuron membrane
Increase number of receptors and promote dendritic branching
Stimulate release of neurotransmitters
Citicoline
Maintain neuron membrane
Increase availability of acetylcholine
Facilitate activity in dopaminergic systems
Piracetam
Facilitate activity in cholinergic, noradrenergic, and dopaminergic systems
Maintain neuron receptors (N-methyl-D-aspartate and cholinergic)
Protect neurons from toxins
Vinpocetine
Increase cerebral blood flow
Increase transport and uptake of glucose
Increase availability of acetylcholine
Acetyl-L-carnitine
Increase neural energy production
Protect neurons from toxins
Maintain neuron receptors
Increase availability of acetylcholine
Antioxidants (e.g., vitamins E and C)
Protect neurons from toxins

plements claimed to have memory benefits. Table 2 summarizes the results of the human studies we report in the sections that follow.

PHOSPHATIDYLSERINE

In recent years, PS has created excitement as a potential "brain-specific" nutrient to help older adults improve declining memory (Crook & Adderly, 1998). It is a naturally occurring phospholipid that is taken into the body as part of the normal diet. Phospholipids are a major component of biological membranes. PS is a minor percentage of the phospholipids that compose biological membranes, but may be especially important in determining neuronal membrane surface potential (the electrical potential at the membrane) and local ionic environment (the mix of electrically charged particles within the neuron; Blusztajn, Richardson, Liscovitch, Mauron, & Wurtman, 1987). Thus, PS is informally characterized as a brain-specific nutrient because of its possible importance in neuronal functioning. Like ginkgo, PS can be purchased as an over-the-counter supplement in many groceries and drugstores. PS has stimulated significant interest in Italy as a treatment for age-associated and dementia-related memory impairment and is featured in a tradebook as a memory cure for age-associated memory impairment (Crook & Adderly, 1998). How might PS promote memory functioning?

Mechanisms and Animal Studies

PS is thought to be especially vital to the neuron membrane. This membrane is particularly important for the communication between neurons. Recall that networks of communicating neurons store memories. Some areas of the neuron membrane contain receptors responsible for receiving the neurotransmitter message from other neurons. Other parts of the neuron membrane allow the neuron to pass the message from one end of the neuron to the other. This process is a truly fascinating one in which the cell membrane essentially transmits an electrical current from one end of itself to the other.

The problem is that as people age, the neuronal membrane changes somewhat in its composition and starts to lose receptors. Also, the receptors that are left begin to lose the capacity to receive messages. It is also possible that the membrane begins to become more "rigid," so that it cannot easily transmit the electrical charge along the neuron. It is easy to see that if these problems become too severe, neurons simply will not pass on the messages they receive. When communication among neurons is compromised, the neuron networks that store memories will fail, and memory will decline. PS seems to help the neuronal membrane resist these age-related changes in its composition, and possibly even to revitalize itself so that it can reverse some of them.

PS within the neuronal membrane is especially important for the activation of a particular kinase—protein kinase C (PKC)—that plays a critical role in learning and memory. As already mentioned, the binding of a neurotransmitter to certain receptors initiates the production of second messengers within the neuron. One of these second messengers acts on PKC within the cytoplasm of the neuron to induce it to move to the cell membrane, where it becomes activated by binding with calcium and PS. That is, PS within the membrane is necessary to activate PKC.

PKC has many functions within the neuron, including the activation of genes that are critical in producing the long-term changes involved in memory. PKC also is involved in regulating the release of neurotransmitters from neurons, another critical aspect of the neural process that underlies cognitive function. Neurotransmitter molecules are held in organelles called synaptic vesicles, with several thousand molecules being in a single vesicle. These vesicles are loaded into specialized release sites in the axon terminals called active zones. To release transmitter from the neuron, the vesicle must move up to and fuse with the neuron's cell membrane, a process called exocytosis. This process is quite complex and involves a large number of proteins. PKC regulates the functioning of a number of these proteins, and so regulates the release of many different types of transmitters, one of which is ACh. It is noteworthy that PKC activity declines with age (Pascale, Govoni, & Battaini, 1998), perhaps because of age-related deficits in PS.

Research with aging animals has shown that long-term treatment with dietary PS attenuates and perhaps even eliminates many of the neuronal effects of aging. For example, we noted earlier that the growth of dendritic spines is a key substrate of stable long-term memory. There is a loss of dendritic spines with aging, and this loss is prevented by dietary PS (Nunzi, Milan, Guidolin, & Toffano, 1987). Treatment with PS has also been reported to counteract the reduction in release of neurotransmitters (e.g., ACh, dopamine, and norepinephrine) that occurs with aging (Casamenti, Scali, & Pepeu, 1991).

Aging not only reduces the amount of neurotransmitter released by neurons, but can also lead to reductions in the numbers of receptors that are present on the membrane surface to receive the neurotransmitter message. This is likely due to reductions in the expression of the genes that code for receptors, a reduction that could easily be caused by reductions in kinase (e.g., PKC) activity. Interestingly, PS has been shown to restore receptor numbers to normal in aged mice (Cohen & Müller, 1992). Also, PS seems to help the neuron membrane maintain its charged state (Blusztajn et al., 1987) so that it can transmit its electrical message. Finally, PS may be important for maintaining the general structure and health of the neuron (Blusztajn et al., 1987; Toffano, 1987). Simply put, PS supplements might have beneficial effects on memory by allowing neurons in the neuron networks to keep effectively communicating with one another so that existing memories can be retained and new memories formed. The theory is that as people age, they need to supplement the brain with more PS than they get through their normal diets.

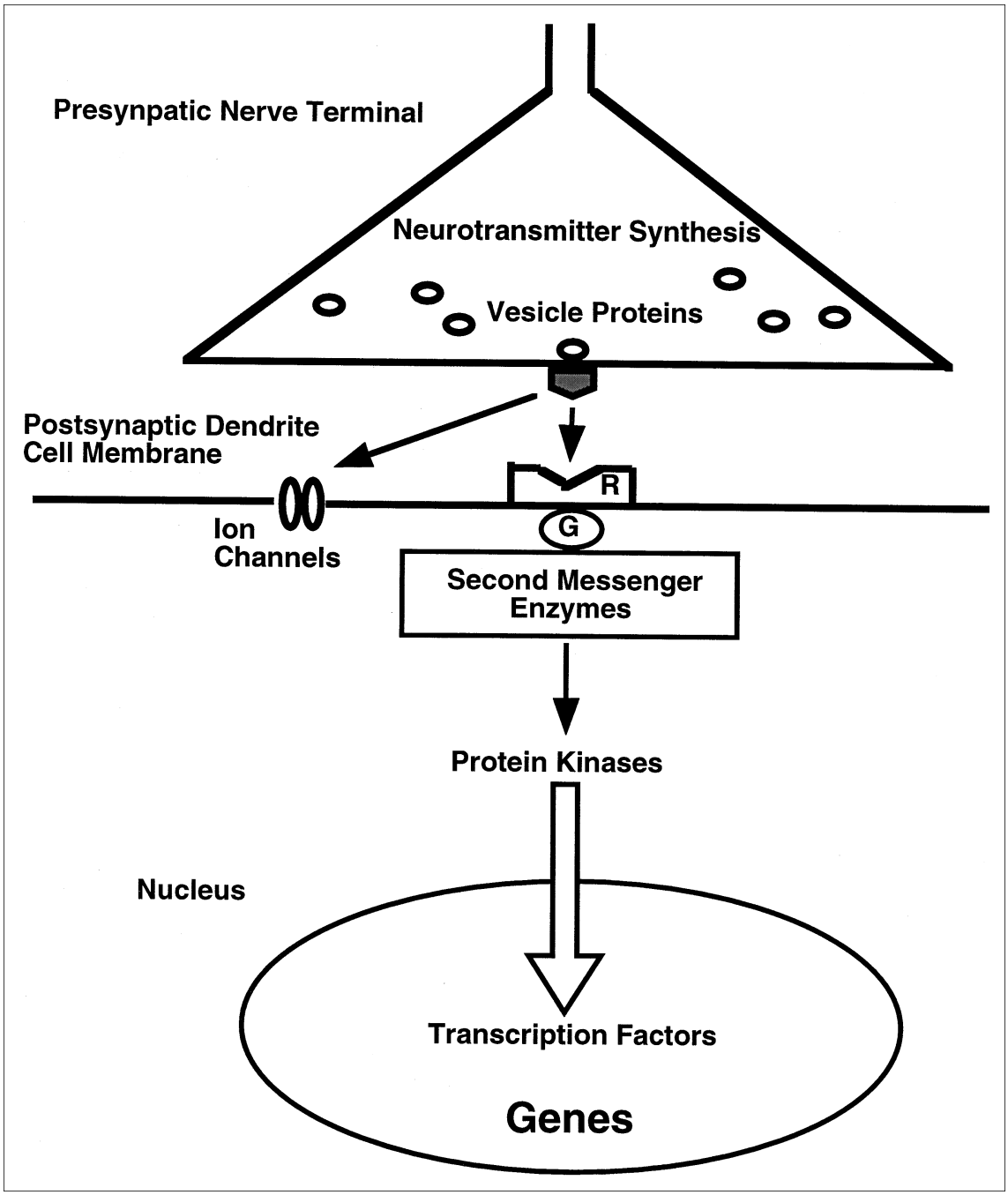

Fig. 2. Illustration of how two neurons communicate. In the neuron that sends the "message" (i.e., the presynaptic neuron), neurotransmitters (the chemical messengers that communicate between neurons) are synthesized and packaged into vesicles. These vesicles are located at terminals at the ends of the neuron's axon. If the neuron becomes sufficiently depolarized, the transmitter molecules are extruded across the cell membrane and enter the space between this neuron and neurons nearby (the synaptic cleft). The transmitter molecules then bind to receptors on the surface of these postsynaptic neurons (dendrites). There are two main types of receptors: ion-channel and G-protein-coupled receptors (R). The binding of a transmitter to an ion-channel receptor leads the channel to open, allowing specific ions to enter the neuron across the membrane. This is the way in which rapid changes in the postsynaptic neuron are produced. The binding of a transmitter to the surface of a G-protein-coupled receptor leads to alterations in the state of proteins (G) that are coupled to the receptor. This alteration then leads to the production of second-messenger molecules, which can exert both immediate and more prolonged effects on the neuron. For example, as illustrated, these messengers can lead to the activation of substances called protein kinases. These protein kinases can, in turn, enter the nucleus of the neuron and act on transcription factors that regulate the transcription of DNA into RNA. Thus, activation of these receptors can alter the genes that are expressed by the postsynaptic neuron, thereby producing the long-term changes that are involved in memory.

Table 2. *Summary of human experimental findings*

Study	Dose and duration	Subject population (age)	Number of subjects	Results
Phosphatidylserine (PS)				
Cenacchi et al. (1993)	300 mg/day 6 months	Older adults (over 65) with moderate-severe cognitive impairment, MMSE = 10–23	388	PS > placebo for word-list recall
Crook et al. (1991)	300 mg/day 3 months	Normally aging adults (50–75), MMSE = 27 or higher	149	PS > placebo for face recognition; PS = placebo at end of treatment for name-face learning and recall (PS > placebo midway through treatment); PS = placebo for telephone-number recall, recall of misplaced objects, and story recall
		("Impaired memory" subgroup)	(57)	(PS > placebo at end of treatment for name-face learning and recall, story recall)
Crook et al. (1992)	300 mg/day 3 months	Older adults (55–85) with probable Alzheimer's disease, MMSE = 12–23	51	PS = placebo for 10 tests from psychometric memory battery
Engel et al. (1992)	300 mg/day 2 months	Older adults (55–75) with primary degenerative dementia, MMSE = 15–27	33	PS = placebo for associative learning, story recall, and immediate visual recall of geometric figures
Palmieri et al. (1987)	300 mg/day 2 months	Older adults (55–80) with moderate cognitive deterioration	87	PS > placebo for word-list recall; PS = placebo for forward digit span
Villardita et al. (1987)	300 mg/day 3 months	Older adults (55–80) with cognitive deterioration, MMSE = 14–23	170	PS > placebo for immediate word-list recall, forward and backward digit span, immediate and delayed semantic verbal memory; PS = placebo for delayed word-list recall and immediate and delayed visual memory
Citicoline				
Agnoli et al. (1989)	1,000 mg/day 6 weeks	Older adults (M = 72) with primary memory impairment, mean MMSE = 20.7	84	Citicoline > placebo for Acquisition Efficiency factor for patients with lower initial deficits; Citicoline = placebo for Encoding and Organization, Cognitive Efficiency factors
Spiers et al. (1996)	1,000 mg/day 3 months	Normally aging adults (50–85), MMSE = 26 or higher	94	Citicoline = placebo for immediate and delayed prose recall
	(2,000 mg/day 2 months)	("Inefficient memory" subgroup)	(27)	(Citicoline > placebo for immediate and delayed prose recall)
Piracetam (PIR)				
Abuzzahab et al. (1977)	2.4 g/day 2 months	Hospitalized geriatric patients (65–80) with mild cognitive deterioration	50	PIR = placebo for immediate visual recall of geometric figures and designs and immediate story recall
Chaudhry et al. (1992)	2.4 g/day 5 weeks	Epileptic patients (10–50); nonpatient control group	75	PIR, but not antiepileptics, improved patients to level of nonpatients on picture recall

Continued

Table 2. *Continued*

Study	Dose and duration	Subject population (age)	Number of subjects	Results
Croisile et al. (1993)	8 g/day 12 months	Adults (57–81) with probable Alzheimer's disease, MMSE = 15–20	30	PIR significantly reduced decline for recognition and recall (for name) of drawings, sentence recall, and story recall; PIR = placebo for recall of complex figures, forward and backward digit span, general knowledge questions
Growdon et al. (1986)	6.6 g/day 2 weeks OR 2.4–9.9 g/day + lecithin 4 weeks OR 4.8–7.2 g/day + lecithin 3 weeks	Adults (56–75) with probable Alzheimer's disease	18	PIR > placebo for 3-week, 4.8 g + lecithin treatment on backward nonverbal span (7 patients); PIR = placebo for every treatment for Brown/Peterson STM, forward and backward digit span, forward nonverbal (block) span, immediate and delayed paired-associate learning for both nonverbal and verbal stimuli, word recognition, story recall (except placebo > PIR for 4-week treatment on immediate story recall)
Israel et al. (1994)	2.4 g/day + memory training OR 4.8 g/day + memory training 12 weeks	Older adults (over 54) with age-associated memory impairment	135	PIR > placebo (with memory training) in terms of improvement over baseline for immediate free recall, high dose of PIR > placebo for delayed free recall; PIR = placebo for Rey word memory test
R.C. Smith et al. (1984)	4.8 g/day + lecithin 12 weeks	Adults (M = 67.1) with probable Alzheimer's disease	11	PIR = placebo for long-term recall; PIR (6/11 improve) > placebo (4/11 improve) for total recall[a]
Vinpocetine				
Balestreri et al. (1987)	30 mg/day 1 month, 15 mg/day 2 months (3 months total)	Older adults (57–94) with chronic vascular cerebral dysfunction	80	Vinpocetine > placebo on MMSQ and cognitive factor of SCAG
Hindmarch et al. (1991)	30 mg/day OR 60 mg/day 16 weeks	Older adults (60 or over) with mild-moderate dementia	165	Vinpocetine (30 and 60 mg) > placebo on Short Cognitive Performance Test
Manconi et al. (1986)	30 mg/day 1 month, 15 mg/day 2 months (3 months total)	Adults (39–81) with degenerative central nervous system disorders, primarily of a cerebrovascular nature	40	Vinpocetine > placebo on MMSQ and cognitive factor of SCAG (one-tailed tests)
Subhan & Hindmarch (1985)	10 mg/day OR 20 mg/day OR 40 mg/day 3 days	Healthy female adults (25–40)	12	Vinpocetine (40 mg) > placebo for reaction time on STM Scan; Vinpocetine (10, 20 mg) = placebo for reaction time on STM Scan; Vinpocetine (all doses) = placebo on choice reaction time
Acetyl-L-carnitine (ALC)				
Livingston et al. (1991)	2 g/day 6 months	Adults (65 or over) with probable or possible Alzheimer's disease, mean MMSE = 16	57	ALC > placebo in terms of improvement over baseline for word recognition; ALC = placebo for picture recognition, name and object learning
Rai et al. (1990)	1 g/day 6 months	Adults (over 60) with probable Alzheimer's disease	20	ALC = placebo for STM of digits, digit span, name and object learning

Continued

Table 2. *Continued*

Study	Dose and duration	Subject population (age)	Number of subjects	Results
Spagnoli et al. (1991)	2 g/day 12 months	Adults (over 40) with probable Alzheimer's disease	108	ALC > placebo for word-list recall, Raven's matrices, verbal judgment and mental calculation test, and visual search of digits (in analysis of covariance); ALC = placebo for story recall, memory for spatial information, reproduction of geometric forms, verbal comprehension, and lexical organization
Tempesta et al. (1990)	2 g/day 3 months	Alcohol-dependent patients (M = 48.3) abstinent for 1 month	55	ALC > placebo for Rey delayed word memory and story recall; ALC = placebo for Rey immediate word recall, visual memory, forward and backward digit span
Thal et al. (1996)	3 g/day 12 months	Adults (50 or over) with probable Alzheimer's disease, MMSE = 13–26	417	ALC = placebo on ADAS-Cog
Thal et al. (2000)	3 g/day 12 months	Adults (45–65) with probable early-onset Alzheimer's disease, MMSE = 12–26	167	ALC > placebo on MMSE attention item; ALC = placebo on ADAS-Cog
Antioxidants—Vitamin E				
Kieburtz et al. (1994)	2,000 IU/day 14 months (on average)	Adults (younger than 80, M = 61) with early Parkinson's disease, MMSE = 23 or higher	348	Vitamin E = placebo in immediate and delayed word-list recall, forward and backward digit span, and MMSE
Sano et al. (1997)	2,000 IU/day 2 years	Adults (M = 73) with probable Alzheimer's disease, mean MMSE = 12.3	169	Vitamin E = placebo on ADAS-Cog and MMSE
Antioxidants—Vitamins E and C				
Benton et al. (1995)	100 mg/day of E + 600 mg/day of C 1 year	College students (17–27)	127	Vitamins E and C = placebo on continuous attention, reaction time, and digit symbol substitution

Note. ADAS-Cog = Alzheimer's Disease Assessment Scale–Cognitive Subscale; MMSE = Mini-Mental State Examination; MMSQ = Mini-Mental Status Questionnaire; SCAG = Sandoz Clinical Assessment–Geriatric scale; STM = short-term memory.

[a]Descriptive comparison of distributions of improvements and declines over baseline under PIR and placebo.

Long-term treatment with PS has been reported to restore normal memory in aged animals on a variety of tasks. Aged animals show declines in learning and memory on a wide spectrum of tasks, and PS treatment has been broadly effective. For example, a task called the Morris water maze is used in many studies of aging. In this task, a rat or a mouse is placed in a circular tank of water that has been made opaque. A platform is placed in the tank, but its surface is a few centimeters below the surface of the water so that it is not visible. Rats and mice do not like being in water, and so the animal swims about the tank in an effort to find an escape route. It will, by accident, encounter the platform and climb onto it, thereby escaping the water. The animal is allowed to stay on the platform for a period of time, and then placed in the water again. The platform is always in the same location, and on succeeding trials the rat or mouse is started in different locations within the tank. The outcome is that the animal learns the spatial location of the platform by using cues within the room in which the tank is located, and swims directly to the platform no matter where in the tank the animal is placed. A large amount of research has shown that the rat or mouse forms a spatial map of the maze that it uses to guide its escape, and this map is retained in memory. The animal can be tested days after training, and it will swim right to the hidden platform. The Morris water maze is of

special interest because it is very sensitive to the functioning of a particular part of the brain called the hippocampus, a region that is especially vulnerable to age-related declines. Thus, an animal with damage to the hippocampus cannot learn and remember this task. Aging is associated with severe deficits in learning and remembering this task, and these are reversed by PS treatment (Zanotti, Valzelli, & Toffano, 1989).

Controlled Human Studies

Effects on patients with moderate cognitive impairments

A handful of double-blind, placebo-controlled, multicenter experiments examining the effects of PS on memory performance in older humans have been conducted in Italy (Cenacchi, Bertoldin, Farina, Fiori, & Crepaldi, 1993; Palmieri et al., 1987; Villardita, Grioli, Salmeri, Nicoletti, & Pennisi, 1987). The subjects in these studies were older adult patients ranging in age generally from 55 to 80 years and displaying moderate cognitive decline as assessed by standard screening tests. Patients with concomitant severe medical conditions, such as depression, chronic alcoholism, and severe Alzheimer's disease, were excluded, as were patients who were taking medications that might mask or interfere with the possible effects of PS (e.g., other nootropic drugs, barbiturates, antidepressants, antipsychotics). At each center, patients were randomly assigned either to treatment with 300 mg of PS per day (divided into three daily doses of 100 mg each) or to placebo treatment (e.g., corn oil) for periods ranging from 8 to 24 weeks. Sample sizes were reasonable, ranging from 87 patients (Palmieri et al.) to 388 (Cenacchi et al.).

Memory tests were administered prior to treatment, at the conclusion of treatment, and usually at the midpoint of treatment. The various experiments used similar though not identical tasks measuring immediate and delayed recall. Short lists of words (5–15) were first auditorily presented at brisk rates (usually 1 word every 2 s). Usually the list (or nonrecalled items of the list) was re-presented to allow multiple recall trials, and a total recall score, representing combined performance across all trials, was calculated. Typically the pretreatment recall levels were used as a covariate, providing a sensitive evaluation of treatment effects.

In all these experiments, PS consistently and significantly improved total recall relative to the placebo treatment for this subject population. However, the effects were also uniformly modest. More precisely, across the studies the proportion of words recalled for the placebo groups ranged from .36 to .60. The PS treatment increased the proportion of recall by just under .03 to just over .06 across the studies. This proportion translates into an increase in total recall of between one and two words. In one case, this increase was the result of a dynamic whereby the placebo group's recall decreased by less than a word from pretreatment to the end of treatment, and the PS group's recall increased by less than a word (Villardita et al., 1987).

Villardita et al. (1987) also reported significant benefits of PS for digit span (recall of digit lists in either forward or backward order; Palmieri et al., 1987, did not find significant benefits for digit span) and for immediate and delayed "cued semantic verbal memory" tests in which semantically related cues were apparently provided to prompt retrieval of words. Other memory tests in this study did not uniformly show a significant advantage of PS. Briefly, the PS and placebo groups showed no significant difference in immediate and delayed recall of geometric figures or in delayed recall of a 15-item list.

This pattern of no or minimal effects of PS on memory tasks other than immediate recall of lists of items was echoed in two additional studies using small numbers of patients. In one study, conducted in the United States, the patients met criteria for probable Alzheimer's disease (51 patients; Crook, Petrie, Wells, & Massari, 1992), and in the other study, conducted in Germany, they had a diagnosis of primary degenerative dementia (33 patients; Engel et al., 1992). The treatment periods and dosage levels were the same as in the Italian studies. Unlike the Italian researchers, Engel et al. used a design in which each participant was tested once after PS treatment and once after placebo treatment (double crossover design), allowing within-subjects comparison of PS with placebo treatment. In this study, none of the three memory tests, including prose and associative-memory tests, showed benefits of an 8-week 300-mg/day PS treatment regimen.

Similarly, in the study by Crook et al. (1992), none of the 10 objective cognitive and memory tests showed effects of a 12-week 300-mg/day PS treatment. Several of the memory items on an interview-based scale (a clinical global improvement scale) showed a benefit of PS treatment. For a subsample of 33 patients with mildest impairment (scores of 19–23 on the Mini-Mental State Examination, MMSE; lower scores on this measure indicate more severe deficits), only a single objective test (one that involved associating first and last names) showed a significant benefit of PS at the end of the 3-month treatment period (though again, several memory-related scale items showed benefits of PS). Clearly, as the authors acknowledged, the interpretation of this effect is clouded by concerns about the large number of comparisons conducted. Given that they used a p value of .05, rather than a more stringent value, for establishing significance, the probability of a Type I error (concluding that a difference exists when it does not) was relatively high.

In summary, among older adults with cognitive impairment that can be considered moderate, PS has produced consistently modest increases in memory performance for a particular recall paradigm (quick presentation of relatively short lists of items). There is little evidence of positive memory effects on other memory tests. From all these studies, only one positive mnemonic effect of PS that could be characterized as sizable emerged. For the cued semantic verbal memory test, the PS group recalled about 50% more items than the placebo group after 3 months of treatment (proportion of items recalled was .64 vs. .44; Villardita et al., 1987).

Effects on normal older adults

In a double-blind, placebo-controlled, multicenter study, Crook et al. (1991) investigated the mnemonic effects of PS in a sample of 149 normally aging adults ranging in age from 50 to 75 years. The participants were considered to have age-associated memory impairment (i.e., memory decline associated with normal aging). People with dementia, Alzheimer's disease, or other neurological disorders associated with cognitive deterioration were excluded from the study. Another feature of this study is that memory testing was conducted 4 weeks after the end of the 12-week treatment, as well as during the treatment (at 3 weeks, 6 weeks, 9 weeks, and 12 weeks). Five memory tests related to everyday memory use constituted the primary memory evaluation: learning of name-face associations, delayed recall of the name-face associations, face recognition, telephone-number recall, and recall of misplaced objects. The authors designated these tests as primary on the basis of normative data showing that these tests produce a clear pattern of age-related decline in performance. Several other memory tests that did not show such clear age-related decline were used as well and were designated as secondary (e.g., story recall).

Overall, the PS treatment produced modest effects. Acquisition and delayed recall of name-face associations were significantly improved during the first 6 weeks of treatment, but these differences did not persist during the latter half of the 12-week treatment. Further, these differences were slight in that they represented about a 1-point improvement over a score of just over 9 (1 point was given for every name correctly recalled upon being cued with the face). By the end of the treatment, the PS group significantly outperformed the placebo group on only one test, the face-recognition test.

More consistent and long-lasting effects of PS were observed in a subgroup of 57 participants who performed poorly on pretreatment memory tests but similarly to the other participants on the vocabulary subtest of the Wechsler Adult Intelligence Scale. For these participants, either immediately at the conclusion of the treatment or at testing 4 weeks after treatment, there were significant benefits of PS relative to the control for all the primary memory measures, as well as for story recall. Also, ratings by a psychologist or nurse showed that this cluster of PS-treated participants improved more than the placebo group on several items in a measure of specific cognitive symptoms and overall cognitive status.

Safety

The studies reviewed reported no adverse effects from the PS treatment. In one study, many of the participants were patients on medication, and PS did not interact with any of the pharmaceutical drugs that these patients were taking (Cenacchi et al., 1993). However, patients taking antipsychotics, antidepressants, barbiturates, methyl-dopa, reserpine, and bromocriptine were excluded from the study. Thus, there is no evaluation of possible interactions of PS with all potential pharmaceuticals taken by adults. Crook and Adderly (1998) recommended against taking PS during pregnancy or lactation and cautioned that individuals taking anticoagulant medication should be careful with PS.

One major safety-related issue concerns the source of the PS. Most studies used bovine PS, but concerns have since been raised about the possibility of viral contamination of that source. Accordingly, PS derived from soy lecithin is now being sold. One possible controversy is whether plant-derived PS has the same effects as animal-derived PS, although Crook and Adderly (1998, p. 86; see also Kidd, 1999) suggested that soy-based and bovine PS produce similar mnemonic effects.

Summary

On the basis of the studies just reviewed, clinical studies without double-blind controls, and clinical observation, some psychologists and medical professionals advocate the use of PS, sometimes along with other supplements like ginkgo, for preventing or reversing memory loss associated with age and age-related dementias (Crook & Adderly, 1998; Goldman, Klatz, & Berger, 1999; Khalsa, 1998; Kidd, 1999). Some researchers are quite optimistic about the effects of PS. For example, Crook and Adderly (1998) concluded that "PS is effective in delaying and usually reversing age-associated memory impairment" (p. 86). In a review of nutrients for restoring cognitive function, Kidd (1999) claimed that "PS is a phospholipid validated through double-blind trials for improving memory, learning, concentration, word recall, and mood in middle-aged and elderly subjects with dementia or age-related cognitive decline" (p. 144).

In light of the studies just reviewed, we believe that these are overly generous interpretations of the scientific evidence. PS does produce effects in the mammalian brain that enhance brain functioning, and it attenuates age-related deficits in learning and memory in a variety of animal paradigms. However, the documented mnemonic effects for PS in humans are limited in a number of critical ways. First, the corpus of studies is small. Second, within this small set of studies, the effects of PS are not consistent across different population groups nor across different types of memory tests. Third, a number of the reported memory increases after PS treatment, though statistically significant, are modest. We are not convinced that the modest increases found would necessarily translate into noticeable differences in memory functioning. Finally, relatively robust effects of PS, in terms of both the degree and the consistency of the improvement across a number of memory tests, seem limited to just one small sample of older adults who had no diagnosed dementias, showed relatively more age-associated memory decline than their peers, were relatively well educated, and scored higher than average on subtests of IQ batteries (Crook et al., 1991).

These cautionary remarks notwithstanding, in our opinion these preliminary findings are strong enough to warrant further

study and suggest possible foci for investigation. Older adults with relatively severe age-associated memory decline might be fruitfully singled out for further study of possible benefits of PS. More judicious selection of memory tests might be warranted as well. The list-recall paradigm appears to be consistently sensitive to PS effects. Reliable replications of these results would provide a foothold from which to explore and analyze benefits of PS. Failure to find consistent effects on memory in some studies may be due to insensitivity in the memory tests used (cf. Crook et al., 1991) or to using tests that do not articulate with the specific memory processes that PS may influence (cf. Hirshman et al., in press). Clearly, most, if not all, of the questions concerning possible memory benefits of PS remain unanswered. We cannot rule out the possibility that PS enhances memory for at least some older adults with memory impairment, but we also cannot confidently conclude that PS has specific positive effects on memory.

CHOLINE

Choline is used to produce ACh. At the start of this report, we mentioned that important neuronal circuits involved in memory depend on this neurotransmitter. ACh appears to decline with age, and impairments that devastate memory (e.g., Alzheimer's disease) largely wipe out the ACh-rich neurons. Choline is found in a number of safe chemical compounds, including phosphatidylcholine (PC), of which a major source is lecithin, and citicoline. PC is the primary dietary source of choline, and is a central substance in the neuronal membrane (Growdon, 1987; Spiers, Myers, Hochanadel, Lieberman, & Wurtman, 1996). Both sources of choline can be purchased as nutritional supplements, and some manufacturers have even boosted their foods with PC (by adding lecithin). With appropriate dosages, these nutrients can find their way into the cells so that the cells do in fact have more of the nutrient.

Mechanisms and Animal Studies

The general idea behind use of choline as a memory booster is that more ACh could be produced if the brain had more of the ingredient (choline) needed to make ACh. The primary source of choline for central cholinergic neurons (i.e., neurons using ACh) is from blood circulation. Circulating levels of choline are in turn determined by its synthesis in the liver and by dietary intake (see Wecker, 1989). Because normal diets contain small amounts of choline (J.J. Wurtman, 1979), augmenting the intake of free choline might affect the available precursor for synthesizing additional ACh. Moreover, the theory is that, as the number of neurons diminishes because of disease or age, the remaining neurons function more effectively if there is more ACh available for transmitting messages. This line of reasoning has produced great interest in the possibility that choline supplements might improve memory.

An experiment that investigated the effects of varying dietary choline in rats does not completely support this theoretical reasoning. The rats were provided a choline-deficient diet, a standard choline-containing diet, or a diet with 10 times more choline than the standard diet (Wecker, 1989). The rats on the choline-deficit diet showed less release of choline from brain slices and lower spontaneous synthesis of ACh than the rats on the standard diet. The rats on the choline-supplement diet did show increased availability of choline in the brain, but this increase did not increase the synthesis of ACh (*in vitro*). Still, one idea is that dietary sources of choline may promote and support increased ACh synthesis under conditions in which cholinergic neurons are firing rapidly (R.J. Wurtman, Hefti, & Melamed, 1981).

It is also possible that the decline in ACh that occurs with aging is not due to reductions in choline, but rather is due to other processes that regulate ACh function. For example, we have already noted that a reduction in PKC activity would reduce ACh release, and an increase in dietary choline would not alter age-related reductions in PKC.

A cytidine-choline compound (citicoline) may produce benefits that go beyond the hypothesized benefits of choline alone. Some researchers have suggested that citicoline may promote neurotransmission of the dopamine neurotransmitter (Fonlupt, Martinet, & Pacheco, 1985) and may facilitate the formation of neural membrane. The two components of citicoline (choline and cytidine) together enhance synthesis of membrane phospholipids in rat neural tissue (Savci & Wurtman, 1995) and in whole brains (Lopez, Agut, Ortiz, & Wurtman, 1992). Phospholipids play an important role in cellular structure and in a variety of cellular activities.

Controlled Human Studies

Phosphatidylcholine

PC (typically administered as lecithin) has been extensively tested for its effectiveness in treating Alzheimer's disease. Because reviews of this research are available, we summarize the conclusions very briefly. Becker and Giacobini (1988) and Growdon (1987) reported that the results of studies examining the efficacy of PC were uniformly negative. In only 2 reports (out of 29) was there evidence for memory improvement in patients with Alzheimer's disease (see Becker & Giacobini, 1988, Table 2). One unpublished study found that PC significantly enhanced the speed of learning nonsense syllables, but primarily for older adults who were slow learners relative to their peers (Ladd & Sommer, 1990). Thus, the research does not strongly support the idea that PC supplements will generally ameliorate memory deterioration for patients with probable Alzheimer's disease. The issue remains open for older adults without serious degenerative neural disease.

Citicoline

Agnoli, Bruno, and Fioravanti (1989) conducted an initial double-blind, placebo-controlled study investigating the effects of a 42-day, 1,000-mg/day citicoline treatment on memory per-

formance in 84 older adults averaging 72 years of age. These adults had complained of mild to moderate memory problems. They scored an average of 20.7 on the MMSE, suggesting they were experiencing dementia-related decline rather than normal age-associated memory impairment (for which scores of 27 or higher on the MMSE have typically been required; Crook et al., 1991). In this sample, citicoline treatment significantly improved performance on an Acquisition Efficiency factor among high-IQ individuals only, but it did not improve their performance on two other factors extracted from the memory testing (Encoding and Organization, Cognitive Efficiency).

Stimulated by the findings of Agnoli et al. (1989), Spiers et al. (1996) administered 1,000 mg per day of citicoline to a group of 94 normal adults for 90 days. The participants ranged in age from 50 to 85 and did not display evidence of pathological memory impairment or age-associated memory impairment. Spiers et al. asked them to recall an unfamiliar story and used the number of ideas recalled as the measure of memory. For the sample as a whole, citicoline did not produce significant memory improvement on immediate or delayed testing relative to a placebo. But in a follow-up with 27 of the same subjects who had scored lower than their peers on immediate story recall (prior to treatment), a higher dose of 2,000 mg/day produced striking benefits to memory. Citicoline improved immediate and delayed prose recall relative to baseline, whereas the placebo generally did not produce a significant improvement relative to baseline. About 9 of the ideas from the story (averaging over immediate and delayed recall) were recalled in the placebo condition, and about 14 ideas were recalled in the citicoline condition, for a gain of more than 50%. Though these results are encouraging, only one type of memory test was used, and very few (27) participants were tested. Moreover, these subjects had worse memory than their peers, and most were over 70 years of age. Spiers et al. suggested, however, that these results for subjects with low pretreatment story recall are consistent with the results of Agnoli et al.

A further interesting feature of the study by Spiers et al. (1996) is that they confirmed plasma choline levels were significantly higher in the citicoline group than the placebo group. The authors argued that this finding is consistent with the idea that changes in brain metabolism related to ACh and PC may underlie the observed mnemonic benefits of citicoline.

Safety

Spiers et al. (1996) reported the following health complaints in their study: insomnia, stomach distress, headache, rash, and cardiac anomalies (e.g., palpitations). Subjects in the placebo condition reported (nonsignificantly) more complaints than those in the citicoline condition. No citicoline-related effects that required medical intervention, termination from the study, or report to the Food and Drug Administration were reported. This pattern is in line with oral-dose-tolerance studies suggesting that citicoline is well tolerated and safe (Dinsdale et al., 1983), with perhaps only infrequent, minor side effects.

Summary

The evidence supporting memory benefits for cholinelike substances is minimal, and not all choline supplements appear to produce positive memory effects. Given the limited evidence available, citicoline seems the most promising choline treatment, although thus far the only memory benefit reported for this compound was found with older adults who had more than usual memory decline. This positive effect for memory-impaired older adults has not been replicated and must be considered very preliminary. Nevertheless, a variety of choline substances are still included in some supplements advertised to substantially boost mental alertness and cognitive functioning.

PIRACETAM

Piracetam, developed in 1967, was the initial compound classified as a nootropic drug. Some people claim that piracetam is the most widely known of the cognitive enhancing agents (Goldman et al., 1999). It is sold under several names, such as Nootropil and Pirroxil, though is not approved by the Food and Drug Administration. In the United States it is obtained for personal use from Europe or Mexico.

Mechanisms and Animal Studies

Piracetam appears to have a number of effects in the brain that could potentially facilitate learning and memory. At a general level, piracetam is said to be a metabolic enhancer (R.C. Smith, Vroulis, Johnson, & Morgan, 1984) and to improve neuronal efficiency or restore impaired neurotransmission (Growdon, Corkin, Huff, & Rosen, 1986). Piracetam may facilitate activity in a number of neurotransmitter systems, including the cholinergic, noradrenergic, and dopaminergic systems (Masotto, Apud, & Racagni, 1985; Nybaeck, Wiesel, & Skett, 1979). In addition, piracetam may combat the age-related decrease in the number of both NMDA (N-methyl-D-aspartate) and cholinergic receptors on the neuronal membrane (Cohen & Müller, 1993), just as do PS and ALC. NMDA receptors are a class of ionotropic receptor especially important in learning and memory. They bind excitatory amino acid neurotransmitters such as glutamate, and their activation is one of the earliest steps in the cellular processes that lead to memory storage.

In terms of more specific biochemical effects, piracetam seems to increase activity of phospholipase A2, an intracellular messenger that is especially important in the production of arachadonic acid within the neuron. In turn, arachadonic acid is converted into prostaglandins, which can modulate neuronal excitability in a very general sort of way and thereby contribute to modulation of synaptic transmission (Gabryel & Trzeciak, 1994). Further, in studies examining neural damage in the rat due to insufficient oxygen in the brain, piracetam has been shown to exert neuroprotective effects. It increases synthesis of phospholipids, which help protect damaged neuronal and other brain membranes. The increase in synthesis of phospholipids

requires high-energy compounds, and piracetam increases energy reserves under reduced oxygen by maintaining normal ATP (adenosine triphosphate) production (Gabryel & Trzeciak, 1994).

Behaviorally, piracetam improves memory in aging mice (Valzelli, Bernasconi, Coen, & Penkov, 1980). These effects appear to be most prominent under experimentally induced brain dysfunction. Studies have also shown that piracetam improves passive avoidance learning (i.e., learning to withhold responses in order to avoid an aversive event; Sara & David-Remacie, 1974; Sara & Lefevre, 1972) and maze learning (Giurgea & Mouravieff-Lesuisse, 1972) in rodents with amnesia induced by electroconvulsive shock or by oxygen deprivation. In mice, piracetam reversed amnesia induced by scopolamine (a drug that blocks a type of ACh receptor; Schindler, Rush, & Fielding, 1984).

The mnemonic effects of piracetam appear to be augmented in rats and mice when it is given in combination with choline (Bartus, Dean, Sherman, Friedman, & Beer, 1981; Platel, Jalfre, Pawelec, Roux, & Porsett, 1984). A possible explanation is that piracetam's effect on the cholinergic system may create demand for a choline source to increase ACh synthesis (see the section on choline).

Controlled Human Studies

Effects on patients with probable Alzheimer's disease

In light of the animal studies reporting positive biochemical and behavioral effects of piracetam on experimentally induced brain dysfunction, investigators have reasoned that piracetam, either alone or in combination with the choline source lecithin (consisting mostly of PC), might be effective for treating the memory deficits associated with Alzheimer's disease. R.C. Smith et al. (1984) conducted an initial double-blind crossover study with 11 Alzheimer's patients (mean age = 67.1) who were given piracetam (4.8 g/day) plus lecithin for 3 months and tested their memory with a multiple-recall-trial procedure in which the same list of words was repeatedly presented (missed items) and recalled (Buschke Selective Reminding Test; Buschke & Fuld, 1974). The numbers of patients who improved and declined (relative to baseline) after the treatment and after the placebo were nonstatistically compared. The number who improved in the two conditions was identical for long-term recall and only slightly favored the piracetam-lecithin treatment for total recall. Nevertheless, the authors concluded that "treatment with piracetam + lecithin may substantially ameliorate selective memory deficits in some patients with DAT [Alzheimer's-type dementia]" (R.C. Smith et al., 1984, p. 544).

A follow-up by Growdon et al. (1986) also tested piracetam with lecithin (as well as piracetam alone) in a double-blind crossover design but included much more extensive memory testing, a variety of doses, and shorter treatment periods (2–4 weeks). This study also generally failed to demonstrate significant benefits of piracetam, either alone or in combination with lecithin. (A significant benefit was found for the 7 patients on 4.8 g/day piracetam plus lecithin for 3 weeks for backward nonverbal span, but the same patients showed no span effect for the 3-week treatment with 7.2 g/day plus lecithin.) A select group of 9 of 18 (total number examined from all conditions) patients who did show some improvement (not necessarily significant) on one or two tests of short-term memory, memory span, paired-associate learning, word recognition, or story recall were continued in an additional crossover study, and even for this group there was no single patient with restored memory functioning after the piracetam-lecithin treatment.

Croisile et al. (1993) extended these initial studies by administering a yearlong treatment of a high dose of piracetam (8 g/day) to 14 subjects with probable Alzheimer's disease and compared their memory performance with that of 16 placebo-treated patients (average age of participants was 66). Both groups generally deteriorated from baseline performance by the end of the 1-year trial on an extensive battery of memory tests including digit span, recall and recognition of visual figures and drawings, story recall, and recall for an incidentally presented sentence. The rate of decline (regression slopes), however, was significantly less extreme for the piracetam group than the placebo group for recognition and recall of drawings and recall of sentences and stories.

Effects in other populations

Piracetam has been tested for its effectiveness in ameliorating memory disturbances in epileptic patients. In a study conducted in Pakistan, epileptic patients ranging in age from 10 to 50 years received 2.4 g/day of piracetam either alone or in combination with an antiepileptic drug, and two additional groups received antiepileptic drugs alone (15 patients per group; Chaudhry, Najam, de Mahieu, Raza, & Ahmad, 1992). At baseline, all groups showed a typical decrement in memory performance relative to a control group of 15 people without epilepsy. After a 5-week treatment, the groups given piracetam, but not the groups given antiepileptics alone, showed improvement on a picture recall task (drawing a picture briefly shown by the experimenter) to levels displayed by the nonpatient control group. IQ subtest scores (Wechsler Intelligence Scale for Children, Wechsler Adult Intelligence Scale) showed a parallel pattern, suggesting that piracetam normalized cognitive function for epileptic patients.

Several other experiments have examined the mnemonic benefits of piracetam for age-related memory decline not necessarily associated with dementia or depression. A 2-month study of hospitalized geriatric patients (65–80 years of age) with mild cognitive deterioration found that a 2.4-g/day treatment of piracetam (25 patients each in the piracetam and placebo groups) had no effect on immediate recall of stories, geometric shapes, and designs (Abuzzahab, Merwin, Zimmerman, & Sherman, 1977).

Another study combined piracetam treatment with a memory training program. Israel, Melac, Milinkevitch, and Dubos (1994) reasoned that a nootropic might positively affect the

neural structures responsible for maintaining memory traces and that improved recall strategies (induced through memory training) would increase the functional value of the neural benefits. Participants were 135 adults age 55 and older ($M = 68.7$) who had consulted a general practitioner for isolated memory problems. None of the adults showed signs of depression or dementia (MMSE scores had to be greater than 26). Forty percent were free of any disease, and 51% were known to have one disease such as arthritis, hypertension, or gastrointestinal problems. During 3 months of treatment, two groups received different doses of piracetam (2.4 g/day and 4.8 g/day), and a third group was given a placebo (45 subjects per group completed the study). All groups additionally received 90 min of memory training once a week for 6 weeks. Half of each group received the training during the first part of the 3-month protocol, and half received training during the last part of the 3-month protocol.

Memory was tested by the Rey Auditory Verbal Learning Test (Rey, 1970) and a free-recall test developed by the principal investigator. Compared with the control group, both piracetam groups showed significantly greater improvement relative to baseline for global recall (immediate and delayed recall averaged) and immediate recall. The high-dose group also showed significantly greater improvement than the control group on delayed recall. When the degree of improvement is considered, the effects of piracetam appear impressive: The high-dose piracetam group that received memory training during the last half of the protocol showed a 35.5% improvement, whereas the placebo group with last-half memory training showed 12% improvement. These effects may be more apparent than real, though, because by chance the placebo group performed somewhat better at baseline than both piracetam groups (by an average of about 1–2 items). By the end of treatment, the three groups were virtually indistinguishable in performance on the free-recall tests. It is possible that had the placebo group's baseline been as low as the piracetam groups', the placebo group would have shown comparable improvement (e.g., as a consequence of memory training). Indeed, the most robust effects were found in the comparison of the two groups that differed the most at baseline: the placebo and the high-dose piracetam group. Further, there were no significant treatment effects on the Rey test, on which baseline performance was nearly identical across the groups.

Safety

In a review of the pharmacology of nootropics, Gabryel and Trzeciak (1994) indicated that piracetam is well tolerated. To our knowledge, side effects have not been reported for the typical doses (2.4–4.8 g/day); that is, in the various studies, participants did not drop out at a higher rate from the drug groups than the placebo groups, nor were there more complaints in the drug groups than the placebo groups. Similar conclusions hold for even higher doses (up to 8 g/day) used with Alzheimer's patients.

Summary

Though used in Europe, Asia, and South America, piracetam is controversial in the United States because of disagreement about its efficacy in improving memory. On the basis of our review of the primary literature, we believe there is reason for skepticism. Studies with older adults with probable pathology (Alzheimer's disease) have not generally found significant mnemonic benefits on an array of memory tests, though the number of subjects sampled has been very low. These failures to find expected benefits have prompted some researchers to suggest that piracetam might be more fruitfully applied to the older range of patients with age-associated memory impairment or Alzheimer's disease (the idea being that in such patients the disease is more prominently involved with cholinergic systems; Growdon et al., 1986).

The results for subjects with age-associated memory impairment also do not clearly support a mnemonic benefit for piracetam. Some anti-aging medical specialists summarized what appears to be the study by Israel et al. (1994) as producing "dramatic results" in relieving age-associated memory impairment (Goldman et al., 1999, pp. 65–66). Yet as we explained earlier, aspects of this study critically cloud its interpretation. Perhaps the most promising study is the one by Chaudhry et al. (1992), which demonstrated an improvement in cognitive functioning of epileptic patients. Regarding this study, it should be noted that reviews have incorrectly reported that the dose was 800 mg/day (cf. Gabryel & Trzeciak, 1994; Goldman et al., 1999), instead of 2.4 g/day (800 mg three times a day).

VINPOCETINE

Vinpocetine is a vinca alkaloid derived from vincamine (extracted from the periwinkle plant). It was developed in Hungary (Thal, Salmon, Lasker, Bower, & Klauber, 1989) and introduced in clinical practice there about 20 years ago, and it has been used to treat patients with loss of cerebral blood flow resulting in cerebral oxygen deficits. Vinpocetine is now more generally promoted as a supplement for cognitive and memory function and considered to be a nootropic (Pepeu & Spignoli, 1989). In one article, a physician indicated that he now recommends vinpocetine as "the most important part of any 'brain-friendly' nutritional supplement" (Schiffer, 1999, p. 25). Vinpocetine is sold alone as a supplement to "help improve memory and concentration" and is a featured ingredient in the product BrainPower. Advertisements claim that vinpocetine is "recommended by pharmacists" and "has been shown to recharge your mind and memory."

Mechanisms and Animal Studies

Vinpocetine increases blood flow in the brain (Schiffer, 1999). It may also increase the transport and uptake of glucose to the neurons. A recent positron emission tomography (PET) study with 12 chronic stroke patients showed that a single-dose

treatment significantly improved the transport of glucose (uptake and release) to the brain, including brain tissue surrounding the damaged area (Szakall et al., 1998). More glucose should help neuronal functioning, including memory performance (see Gold et al., this issue). Both increased blood flow and improved delivery of glucose to neurons should be especially helpful to older adults who have ischemia.

Further, diminished oxygen (due to decreased blood flow) can damage or kill neurons, and memory loss follows if the damage is sufficient. By improving blood flow, vinpocetine may protect against such damage. Using animal models of ischemia, investigators have found neuroprotective effects from vinpocetine. Rischke and Krieglstein (1991) examined hippocampal damage in rats 7 days after experimentally induced cerebral ischemia. Among control rats, 77% of hippocampal neurons were damaged, whereas in rats given 10 mg/kg of vinpocetine (either before or after the ischemia), damage was reduced to 37% of the hippocampal neurons. This neuroprotective effect was replicated and was also found to be dose sensitive, with lower (2 mg/kg) and higher (20 mg/kg) dosages not producing the effects. This study suggests that appropriate medium doses of vinpocetine can reduce the loss of neurons due to decreased blood flow in memory regions of the brain. If the reduction in loss is great enough, then memory impairment might be slowed or avoided. Finally, vinpocetine may increase levels of the ACh neurotransmitter, which is, as we noted earlier, especially important in memory regions of the brain (cf. Schiffer, 1999).

In the single animal study of the effects of vinpocetine on memory, DeNoble (1987) found that vinpocetine enhanced the retrieval of memory for a passive avoidance response. Vinpocetine administered after the response was learned and just before the memory test enhanced performance, thereby suggesting an effect on memory retrieval. Vinpocetine was not tested for its ability to enhance retention per se.

Controlled Human Studies

Effects on patients with cognitive impairments

Three controlled studies investigated vinpocetine with older adults who had memory problems associated with brain dysfunction (either circulation problems in the brain or mild to moderate dementia-related brain disease; Balestreri, Fontuna, & Astengo, 1987; Hindmarch, Fuchs, & Erzigkeit, 1991; Manconi, Binaghi, & Pitzus, 1986). In all the studies, the groups given vinpocetine showed more improvement than the placebo groups for tests measuring attention, concentration, and memory. The size of this improvement for reported scores was noticeable.

In the study by Balestreri et al. (1987), patients taking vinpocetine for 3 months (dosages of 10 mg three times a day for the first 30 days, dropping to 15 mg a day for the last 60 days) significantly improved their scores (17.4 to 20.5) on the Mini-Mental Status Questionnaire (Part A corresponds to the Cognitive Capacity Screening Examination of Jacobs, Bernhard, Delgado, & Strain, 1977, and assesses orientation in time and space, mathematical ability, recent memory, and knowledge of antonyms and synonyms; Part B includes aspects of the MMSE; the total maximum score for both parts is 39), whereas patients taking the placebo showed no improvement. Using an identical dosing regimen, Manconi et al. (1986) found a similar significant improvement of 4.7 points on the Mini-Mental Status Questionnaire (sum of parts A and B), a gain that was significantly different from the 0.4-point drop in the placebo group (one-tailed test). Further, in both studies, vinpocetine produced significantly greater retention of cognitive function relative to baseline as assessed by the cognitive dysfunction items on the Sandoz Clinical Assessment–Geriatric scale.

Significant effects were also reported by Hindmarch et al. (1991). For 16 weeks, patients were given a low dose (30 mg/day, in three 10-mg dosages) of vinpocetine, a high dose (60 mg/day taken in dosages of 20 mg three times a day) of vinpocetine, or a placebo. They were tested with the Short Cognitive Performance Test (SKT; Erzigkeit, 1986) just prior to treatment and at 4-week intervals through the conclusion of treatment. (The SKT assesses cognitive deficits in memory and speed of information processing.) Both vinpocetine-treated groups improved about 4 points on the SKT, whereas the placebo group improved 3 points (all patients had to score at least 9 points on the test before the study began, with higher scores indicating worse performance). The improvements were significantly greater for the vinpocetine groups than for the placebo group (using a one-tailed test). Thus, taking vinpocetine for 16 weeks gave patients about a 1-point advantage in memory and concentration performance on the SKT relative to a placebo.

Vinpocetine had promising effects in terms of global improvement in the illness of the dementia patients in these three studies. Manconi et al. (1986) reported that global ratings indicated 87% of the vinpocetine patients, compared with only 11% of the placebo patients, had improved. In Hindmarch et al. (1991), 21% of the patients given vinpocetine were classified as strongly improved, whereas only 7% of the patients given the placebo pill were classified as strongly improved. Balestreri et al. (1987) found similar positive effects of vinpocetine on rated global improvement. Alzheimer's patients, however, have not shown these effects. In an open-label (patients knew what was being administered) 1-year trial with 15 Alzheimer's patients, using doses increasing from 30 mg/day to 60 mg/day, there was no global improvement, and the decline in word-list recall was comparable to that observed in a nonplacebo control group (Thal et al., 1989).

Effects on normal younger adults

Only one experiment of which we are aware tested healthy younger adults (25–40 years of age), but this study included very few subjects (12), incorporated only a few tests, and used extremely short treatment periods (3 days; Subhan & Hindmarch, 1985). The crossover design did manipulate dosage level (10 mg/day, 20 mg/day, or 40 mg/day). The high dosage

significantly decreased response time in a memory-scanning paradigm in which subjects decided whether a given digit was contained in a previously presented memory set of one to three digits. No effects were reported for a choice reaction time task.

Safety

In these studies, the side effects reported with vinpocetine were not any more extreme than those reported with the placebo pill. On the basis of their study with 15 patients, Thal et al. (1989) concluded that vinpocetine is a safe drug for patients with probable Alzheimer's disease. However, vinpocetine probably should not be taken with blood thinners (anticoagulant medicine). Some of the products sold in stores are in 5-mg doses, with the manufacturer recommending three dosages per day. These dosages are the minimum used in the experimental research, so safety concerns may be minimal, but these dosages also may be too low to provide any mnemonic benefit, if such a benefit exists.

Summary

Because of its positive effects on blood circulation and glucose utilization in the brain, and because of the placebo-controlled research just described, vinpocetine has been identified as a potential supplement for older adults with chronic brain-circulation problems and related dementia. On the plus side, statistically significant improvements on general cognitive and clinical assessment scales have been found in three studies using patients with neural degenerative disorders that were primarily cerebrovascular. However, the effects on memory have been tested minimally, if at all. Thal et al. (1989) found no benefits on word-list recall in their small-scale open-label study using Alzheimer's patients. We conclude that there is evidence for global cognitive improvement, but the research evidence for a specific memory benefit is less strong for vinpocetine than for PS or citicoline.

ACETYL-L-CARNITINE

ALC is an amino acid that is included in some "brain power" supplements sold in health food stores and advertised on radio and in magazines. It can also be purchased as an individual supplement. ALC is found in lists of nutritional agents promoted as producing cognitive benefits for middle-aged and elderly people (e.g., Kidd, 1999). ALC is actively transported across the blood-brain barrier (Thal et al., 1996). It is thought to influence the cholinergic system as a cholinergic receptor agonist (facilitator) and also may promote synthesis and release of ACh (Imperato, Ramacci, & Angelucci, 1989). More generally, ALC participates in cellular energy production and in maintenance of neurons (e.g., receptors) and repair of damage.

Mechanisms and Animal Studies

The most common function of ALC is to aid in the transport of substances across the membrane of mitochondria, thereby participating in the production of energy within the brain (Thal, Calvani, Amato, & Carta, 2000). Mitochondria are scattered throughout the cytoplasm of neurons and other cells and are the site of cellular aerobic respiration. When a mitochondrion "breathes in," it pulls pyruvic acid and oxygen inside. A complex process (the Krebs cycle) then ensues, ultimately producing ATP. The chemical energy stored in ATP is the neuron's energy source, and when a mitochondrion "exhales," ATP is released into the cytoplasm. ATP is especially important in neurons because in a resting human about 40% of total energy consumption is used to operate the "pumps" that keep certain ions (e.g., sodium and potassium) either inside or outside the neurons to regulate their excitability. This is why the brain is so sensitive to damage by oxygen deprivation or reductions in ATP.

ALC has also been shown to have a variety of other neural effects that might be relevant to its potential as a nootropic compound. It can increase PKC activity (Pascale et al., 1994) and reverse the age-related decline in the number of NMDA receptors on the neuron membrane (Castornia, Ambrosini, Pacific, Ramacci, & Angelucci, 1994). In addition, ALC has a variety of other relevant effects on the brain. For example, it can elevate levels of neurotrophins such as nerve growth factor (NGF). The neurotrophins are a family of structurally related proteins that function during development to guide the differentiation and growth of neurons. However, they also participate in the maintenance of adult neurons and are important in the repair of damage. Recently, the neurotrophins have been implicated as key factors in the mediation of neural plasticity and have been shown to be required for the formation of stable memories (McAllister, Katz, & Lo, 1999). This is very likely because the neurotrophins are needed to produce the structural alterations (e.g., the growth of dendritic spines) required for permanent memory.

Given these diverse and important effects on the brain, it should be no surprise that in animal studies ALC has been found to protect central nervous system synapses in neurodegenerative and aging conditions. For example, ALC reduces deficits in brain energy metabolism and phospholipid metabolism (Aureli, Miccheli, & Ricciolini, 1990), likely because it aids mitochondriol function. If we look beyond brain activity to observable behavior, long-term ALC administration in rats increases longevity, improves spatial learning, improves avoidance learning in aged rats, and improves long-term memory performance (Barnes et al., 1990; Ghirardi, Milano, Ramacci, & Angelucci, 1989; Markowska et al., 1990). This evidence provides a basis for the hypothesis that ALC treatment might benefit cognitive and memory functioning in older humans.

Controlled Human Studies

Effects on patients with probable Alzheimer's disease

Nearly all of the human studies have examined the effects of ALC using patients with probable Alzheimer's disease. Two

small-scale studies that used a 24-week trial, with ALC doses ranging from 1 g/day to 2 g/day (cf. Carta & Calvani, 1991), showed nominal advantages for the ALC-treated patients over a range of memory tests, but only one significant effect. In Livingston et al. (1991), ALC patients ($n = 26$) showed improvement on word recognition, whereas control subjects given a placebo ($n = 31$) showed decline, yielding a significant benefit for ALC. Nonsignificant advantages for ALC were also found in picture recognition, object learning, and name learning. Similarly, Rai et al. (1990), with an even smaller sample of patients (7 in the ALC condition and 13 in the placebo condition), found that ALC improved name learning and short-term digit recall, whereas there was decline for the placebo patients. These treatment differences were not statistically significant, however, probably because of low statistical power. For object learning and digit span, no differences between groups were apparent.

Spagnoli et al. (1991) sampled patients diagnosed as having the disease for at least 6 months, evaluating performance with a comprehensive set of memory and cognitive tests. After a year of treatment with 2 g per day, the patients given ALC (52 maximum for any particular measure) showed less decline than the group given the placebo (56 maximum for any particular measure) on some cognitive measures. These differences were not significant, however, for verbal comprehension, lexical organization, ability to copy geometric forms, memory for stories, or long-term memory for spatial information. Only for word-list recall did ALC significantly reduce memory loss relative to the placebo. The most consistent effects were in ratings of performance of everyday activities and habits, as well as personality and interests, which showed the ALC group deteriorated less than the control group.

Other recent large-scale double-blind, placebo-controlled studies have reported minimal or no benefits of ALC in slowing cognitive deterioration with patients diagnosed with probable Alzheimer's disease (Thal et al., 1996, 2000). In these studies, as in Spagnoli et al. (1991), the ALC treatment lasted a year; however, the dosage was elevated to 3 g per day. In a sample of 417 patients age 50 or older, Thal et al. (1996) found that ALC treatment (206 patients) did not significantly attenuate the cognitive impairment (as assessed by the Alzheimer's Disease Assessment Scale–Cognitive Subscale, ADAS-Cog; Mohs, Rosen, & Davis, 1983) observed over the course of the year, relative to the placebo group (211 patients). A more in-depth analysis showed some tantalizing patterns, however (see Brooks, Yesavage, Carta, & Bravi, 1998). When the sample was limited to patients who completed the study and complied with the treatment regimen, ALC produced a significant slowdown in cognitive deterioration relative to the placebo for those patients classified as having early-onset (65 or younger) Alzheimer's disease. There were also trends showing less decline for the ALC group than the placebo group on global clinical scales (e.g., Clinical Global Impression of Severity and Clinical Global Impression of Change). Because these early-onset patients showed more rapid decline than the late-onset patients, these results suggest that ALC may slow the progression of Alzheimer's disease among individuals who would otherwise experience a fast decline.

To follow up the suggestive findings in their earlier study (Thal et al., 1996), Thal et al. (2000) focused exclusively on patients with probable early-onset Alzheimer's disease (45- to 65-year-old patients). In a sample of 167 patients who completed the study (83 in the ALC group and 84 in the placebo group), no significant treatment effects of ALC were found on the ADAS-Cog. ALC did produce significantly less decline than placebo on the MMSE item that the authors claimed pertains to attention. The authors noted that, unexpectedly, this early-onset placebo group did not show unusually rapid decline during the year.

Effects in other populations

A study with 55 alcohol-dependent patients who had been abstinent for 1 month and had deficits on at least two out of six memory and cognitive tests produced mixed results as well (Tempesta et al., 1990). The 29 patients who received 2 g/day of ALC for 12 weeks performed significantly better on long-term word-list memory (Rey delayed recall and recognition) and story recall than the 26 people given placebo. There were no significant differences on forward and backward digit span, visual memory, and the immediate-recall portion of the Rey Auditory Verbal Learning Test.

Safety

ALC is typically well tolerated at dosages normally recommended by manufacturers (1 to 2 g). Similarly, at higher dosages of 3 g per day, no clinically significant adverse effects of ALC were found (Thal et al., 1996, 2000). In one study (Thal et al., 1996), ALC produced incidences of body odor, increased appetite, and rash. One noted possible side effect is increased restlessness and overactivity. For this reason, it is recommended that ALC be taken long before bedtime to avoid agitation during sleeping hours.

Summary

The evidence is sparse, but suggests that a yearlong treatment of 2 to 3 g of ALC daily might slow the behavioral deterioration associated with Alzheimer's disease. The primary significant cognitive benefit was found for a small sample of fast-declining Alzheimer's patients. Effects on psychometric tests of memory and cognitive functioning have generally not been statistically significant, though Spagnoli et al. (1991) reported mixed effects across a variety of cognitive tests, and significant benefits have consistently appeared for word-list memory. Spagnoli et al. suggested that benefits might be better evaluated with less impaired Alzheimer's patients. With subclinically impaired alcoholics, memory benefits were also mixed. Whether

ALC would have mnemonic benefit for aging adults without brain disease is untested as far as we know.

ANTIOXIDANTS

Antioxidants help neutralize free radicals, oxygen molecules lacking electrons. These free radicals, which are produced through normal metabolism, scavenge their missing electrons from other molecules, and in the course of doing so may cause damage to important cell components such as fat, protein, or even DNA. As people age, tissue-damaging free radicals become increasingly prevalent, and many researchers think an inability to buffer the effects of this oxidative stress may be responsible for age-related neuronal decrements (Joseph et al., 1999) and neurodegenerative disease (Quinn & Kaye, 1998). If antioxidants counter the onslaught of damaging free radicals that occurs with aging, and if memory decline is related to oxidative-induced neuronal destruction, then antioxidants might help slow memory decline, and possibly improve memory. Further, because antioxidants have been shown to promote cardiovascular health, and because cardiovascular dysfunction can be related to cognitive and memory impairment, antioxidants may protect against memory decline through this mechanism as well (Perkins et al., 1999).

Vitamins such as E and C (as well as *Ginkgo biloba*; see Gold et al., this issue) are antioxidants that have received attention for possibly having such memory benefits. Practitioners of alternative medicine have long recommended vitamin E to help treat memory loss associated with Alzheimer's disease, and more recently, mainstream health practitioners have been starting to routinely recommend vitamin E for their Alzheimer's patients.

Mechanisms and Animal Studies

The central nervous system is deficient in free-radical protection and thus may be vulnerable to oxidative stress, with the vulnerability increasing with age (Joseph et al., 1996). The basic reason that the brain is so vulnerable to oxidative stress is that it uses a great deal of oxygen to produce the large amount of energy required to maintain the ionic environment of neurons. The deleterious effect of oxidative stress on neurons seems particularly evident in Alzheimer's disease (Finch & Cohen, 1997). For instance, increased oxidative stress causes damage to essential neurofilament proteins and induces cell death in Alzheimer's disease (see Joseph et al., 1999). It thus seems possible that oxidative stress plays a role in Alzheimer's disease and perhaps normal aging as well. Increasing antioxidant levels in the organism might retard or reverse the damaging effects of oxidative stress on neuronal functioning.

Recent studies with aging rats have found that long-term treatment with antioxidant-rich diets can stall the onset of age-related decrements in neural functioning (Joseph et al., 1998, 1999). Recall that activation of metabotropic receptors can lead to long-term changes in neuron function and gene expression, and so is important for the formation of stable memories. There is an age-related decline in the ability of the neural processes controlled by these receptors to respond rapidly to receptor activation, and this decline is reversed by a diet rich in antioxidants (Joseph et al., 1998). Metabotropic receptors span the cell membrane and are coupled to what are called G proteins (so called because they bind guanine nucleotides), which are inside the neural membrane. Occupation of a receptor by the appropriate neurotransmitter activates the G protein on the inside of the neuron, allowing the G protein to initiate the intracellular cascade that produces long-term changes in the neuron. The ability of the G protein to turn on and off rapidly declines with age, and it is this deficiency that is reversed by antioxidants (Joseph et al., 1998).

Joseph et al. (1998) also studied the effects of their experimental diet on neuronal functioning by measuring the ability of neurons to take in calcium. This is a critical feature of neuronal function because calcium regulates neurotransmitter release, as well as many other functions. The dietary treatment Joseph et al. used prevented the decline in calcium uptake (i.e., in neurons' ability to take in calcium) that occurs with aging. As these authors noted, however, it is possible that the positive effects obtained were due to unspecified nutrients other than antioxidants that were also present in the experimental diets. In this regard, it is interesting to note that the control animals and animals on the antioxidant diets had different levels of vitamin E in only one brain area—the hippocampus (Joseph et al., 1999). This is a tantalizing finding, as the hippocampus is thought to be centrally involved in certain types of memory functioning.

Joseph et al. (1999) examined whether antioxidant diets improved the performance of aged rats on the Morris water maze. The rats on the antioxidant diets showed more improvement between Trials 1 and 2 than the control rats, suggesting the antioxidant-fed rats had better memory. The hippocampus plays a prominent role in rats' performance of the water maze task, so together the results of the studies suggest that the memory effects observed may have been related to increased concentrations of vitamin E in the hippocampus.

In sum, the research supports the idea that antioxidants can mitigate the negative effects of oxidative stress on some aspects of neuronal functioning in aged animals. There is also a modest body of work using limited learning and memory paradigms showing that antioxidants can help improve memory performance of older animals. It some cases, it is not entirely clear that these effects were the result of antioxidant mechanisms; nevertheless, there is an empirical motivation for exploring the possible memory benefits of antioxidant supplements, especially for age-related and Alzheimer's-related memory decline.

Controlled Human Studies

Effects on normal younger adults

Benton, Fordy, and Haller (1995) administered vitamin supplements or placebos (double blind) for a year to healthy col-

lege students ranging in age from 17 to 27 (students already taking vitamin supplements and females on oral contraceptives were excluded). The supplements contained 10 times the daily-recommended dose of several vitamins, including the antioxidants C and E (600 mg/day of vitamin C and 100 mg/day of vitamin E). Cognitive performance was assessed at baseline, at 3 months and then either 6 or 9 months after initiation of the treatment, and at the end of the year, with 127 students completing the study. The tests measured attention, vigilance, and response speed. For the females, there were significant interactions between testing time and treatment condition, showing improvement for the vitamin group but not the placebo group. However, at the end of treatment, the differences between the vitamin and placebo groups did not reach significance. There were no significant correlations between changes (from baseline) in blood serum levels of either vitamin C or vitamin E and changes in performance on any of the cognitive tests. This absence of a relationship held for both females and males at 3 months (when the serum levels of the vitamins had reached a plateau), as well as at the 1-year mark.

Effects on patients with brain pathology

Using participants at the other extreme of cognitive functioning, Sano et al. (1997) investigated the effects of vitamin E for patients with probable Alzheimer's disease of moderate severity. In this widely cited 23-center, 2-year experiment, 85 patients were given a dose of 2,000 IU (international units) per day of vitamin E, and 84 patients were given a placebo (double blind). Cognitive functioning was assessed by the ADAS-Cog and the MMSE. Vitamin E did not slow the rate of decline on these tests (i.e., the decrease in performance from baseline to final testing was equivalent for the vitamin E and placebo groups), and had no effects on final scores (mean treatment time was 12.4 months for final ADAS-Cog scores and 15.6 months for final MMSE scores). However, vitamin E showed significant benefits on the Blessed Dementia Scale (Blessed, Tomlinson, & Roth, 1968) and delayed by about 8 months the progression of the disease to certain specified landmarks. For instance, vitamin E significantly delayed the time before patients required institutionalization and the speed at which they lost daily living skills. As the authors noted, cognitive function is required in activities of daily living (also assessed in the Blessed Dementia Scale), so the results may suggest some effect of vitamin E in slowing aspects of cognitive decline in Alzheimer's patients.

The patients in the study by Sano et al. (1997) were more impaired than the patients in some other clinical trials testing Alzheimer's drugs approved by the Food and Drug Administration. Further, the vitamin E group had significantly lower scores (lower functioning) on the MMSE at baseline than the placebo group (11.3 vs. 13.3, respectively), which may have prevented the emergence of effects. Perhaps with older adults with no pathological cognitive impairment, vitamin E would be more efficacious.

Another experiment does not support this possibility, however. Kieburtz et al. (1994) investigated the effects of long-term vitamin E treatment, with a placebo control (whether a double-blind procedure was used is unclear), on memory and cognitive performance for early Parkinson's patients with no signs of dementia (MMSE score of 23 or higher). The patients, who averaged just over 60 years of age, also had no indication of depression and were not taking anti-Parkinson's disease medication. One hundred seventy-four patients were given a vitamin E dose (2,000 IU/day) identical to that Sano et al. (1997) used, and the treatment time was approximately equivalent (average of 14 months). After treatment, these patients and the 174 placebo patients did not perform significantly differently on forward and backward digit span tasks and various indices of list recall. There were also no significant differences between the groups on various other cognitive tests. Corrections were applied to keep the experiment-wise Type I error rate at .05, so the cutoff for observing statistically significant treatment effects on any one measure was quite a bit more stringent than that for other experiments we discuss in this report. Still, the mean differences between the vitamin E and the placebo groups were negligible.

Safety

At recommended doses, antioxidants contained in food sources and vitamin supplements are considered safe. Safety concerns may arise, however, with megadoses of vitamins. The 2,000-IU dosage of vitamin E that had a positive effect of delaying major landmarks of Alzheimer's disease in the study by Sano et al. (1997) is within the range used in attempts to treat some cancers and Parkinson's disease (typical doses are 800–2,000 IU). However, this dosage is considerably higher than the Food and Drug Administration's guideline of 30 IU for normal consumption, as well as the 400 IU recommended by some nutritionists. Very recently, an *in vitro* study with vitamin C showed that it can cause decomposition of lipids, yielding products that produce DNA lesions (Lee, Oe, & Blair, 2001). The authors suggested that an oral dose of 200 mg/day of vitamin C produces *in vivo* concentrations comparable to those in their *in vitro* study, with high oral dosages potentially contributing to "substantial amounts of DNA damage in vivo" (p. 2086). At this point, it is not clear that megadoses of at least certain antioxidants are reasonably safe.

Summary

The theoretical basis suggesting a beneficial effect of antioxidants on neural functioning, especially with regard to neural declines associated with aging, is reasonable. Antioxidants may also improve cardiovascular function, and this may help prevent cardiovascular events that have negative consequences to memory. Consequently, antioxidants would theoretically seem to be useful in forestalling or slowing age-related memory decline. Some animal research supports this idea. To date,

however, the few placebo-controlled human studies of which we are aware have reported no beneficial effects of antioxidant treatment (specifically vitamin E) on attention or memory.

Clearly, the results with humans are too preliminary to justify concluding that antioxidants are not useful for maintaining memory function. Many unexplored issues warrant more research. One issue is that the existing results are based either on healthy college students or on patient groups with moderately severe Alzheimer's disease or early Parkinson's disease. If antioxidants do benefit memory, these effects might emerge in normal older adults with age-associated memory decline.

This possibility is consistent with findings from recent large-scale correlational studies. For instance, in one such study, a multiethnic sample of 4,809 elderly, noninstitutionalized U.S. residents (age 60 and over) learned a list of three words and a three-sentence story (Perkins et al., 1999). Their recall for the words and the story was assessed after they performed a distractor activity and combined into a single memory score. Blood serum levels of various antioxidants (including vitamins A, C, and E) were measured. A multiple regression analysis showed that the demographic variables of sex, alcohol consumption, education, and annual income all related significantly to memory performance. With the variance due to these variables removed, there was a significant positive relation between blood concentration levels of vitamin E (but not the other antioxidants) and memory performance. In Switzerland, Perrig, Perrig, and Stahelin (1997) examined the association between serum levels of antioxidants and memory (recall and recognition of pictorial scenes) and vocabulary performance in 442 healthy older adults aged 65 to 94 (mean of 75). Antioxidants other than vitamin E significantly predicted recognition and vocabulary scores when age, gender, and education were taken into account statistically. Despite the inconsistency in the particular antioxidant that was found to be associated with memory, taken together these correlational analyses provide initial support for the possibility that there is a positive relation between antioxidants and memory in older populations.

A second issue is that in the existing controlled studies with humans, with the exception of Kieburtz et al. (1994), memory functioning per se has been evaluated only minimally, if at all. As just noted, published correlational studies using memory tests have found relationships between antioxidant levels and memory, at least for healthy older adults (see also Goodwin, Goodwin, & Garry, 1983; La Rue et al., 1997). These results suggest the need for more controlled studies that use older adults and focal tests of memory, in addition to or instead of broad-based cognitive-attentional assessments.

A third issue is that because antioxidants work as a system (Perkins et al., 1999), their effectiveness can depend on levels of other vitamins and minerals. Also, intake of an antioxidant may not directly translate to serum levels. Thus, to find reliable memory benefits, researchers may need to be sensitive to levels of other micronutrients, as well as the serum level (rather than intake amount) of the target antioxidant (e.g., see Goodwin et al., 1983). Also, because of these interdependencies, it might be the case that particular antioxidants are more effective than others (cf. Perkins et al., 1999).

Finally, certain neural systems may be particularly affected by aging and particularly vulnerable to lifelong oxidative stress (e.g., see La Rue et al., 1997). Such areas (e.g., the brain's frontal areas) can be related to certain types of cognitive and memory functioning, such as effortful memory tasks. Cognitive and memory tests that are most sensitive to the functioning of these "at risk" neural systems would be most likely to show possible benefits of antioxidants. We amplify on this theme in the next section.

FUTURE WORK AND MORE FINE-GRAINED ANALYSES OF MEMORY

For most of the "brain-specific" nutrients we have reviewed, mildly suggestive effects can be found in preliminary controlled studies. Understandably, these studies have assessed memory with standard psychometric memory assessments or more general tests designed to reveal cognitive impairment that may signal dementia or other pathology. There are hints, however, that a more fine-grained approach that focuses on memory processes rather than on memory tests per se and that is sensitive to particular memory demands may be fruitful for gauging and illuminating effects of drugs and supplements on memory. To illustrate this point, we consider two very recent studies.

Ginkgo-Ginseng

In a study examining possible effects of a ginkgo-ginseng compound, Wesnes, Ward, McGinty, and Petrini (2000) tested 38- to 66-year-old normal adults with no sign of memory-impairing diseases. For 12 weeks, each participant was given either the compound or a placebo pill. Memory testing occurred before the treatment, during the treatment period, and 2 weeks after the treatment was discontinued. The memory tests administered were spatial and numeric working memory, immediate and delayed word recall, and word and picture recognition. Testing was repeated four times throughout each memory-test day, with the first test at 7:30 a.m. and the last test at 2:30 p.m. Across testing times, parallel versions of the tests were administered. This study has caused excitement because after just 4 weeks of treatment, the ginkgo-ginseng group showed significantly more improvement on the memory tests than did the placebo group. Further, this improvement was still present 2 weeks after the treatment had been discontinued (14-week testing).

A more detailed inspection of the results, however, uncovers a potentially critical pattern. Table 3 displays the difference in test performance at Weeks 12 (conclusion of the treatment) and 14 (2 weeks after the conclusion) relative to baseline (Week 0). When testing was at 7:30 a.m., there was little or no difference in memory improvement between the ginkgo-ginseng and pla-

Table 3. *Performance of ginkgo-ginseng and placebo groups in Wesnes, Ward, McGinty, and Petrini (2000)*

		Group			
		Placebo		Ginkgo-ginseng	
Memory test	Week	7:30 a.m.	2:30 p.m.	7:30 a.m.	2:30 p.m.
Spatial working memory	0	85.95	76.35	86.00	72.32
	12	6.77	5.72	4.76	10.78
	14	5.27	4.87	5.23	13.12
Numeric working memory	0	91.80	89.42	92.20	86.94
	12	1.53	4.90	1.93	5.17
	14	1.23	−0.31	2.99	3.55
Immediate word recall	0	34.94	31.07	35.52	29.90
	12	2.41	−1.95	1.97	0.89
	14	2.60	−0.31	3.33	1.28
Delayed word recall	0	20.76	9.08	22.90	8.06
	12	4.18	0.46	3.72	3.12
	14	4.06	−0.57	3.39	5.05
Word recognition	0	56.17	49.96	55.10	46.07
	12	2.07	−0.84	0.15	2.92
	14	0.92	−2.15	0.98	2.05
Picture recognition	0	75.92	70.52	74.10	68.28
	12	1.55	4.42	3.28	1.69
	14	3.45	−0.29	2.54	2.60

Note. For Week 0 (predosing baseline), the table shows the percentage correct on each test. For Weeks 12 and 14, the table shows the change from the baseline score. Week 14 was 2 weeks after treatment was discontinued.

cebo groups: For all the memory tests except numeric working memory, at the end of treatment (or Week 14 for picture recognition) the placebo group showed slightly more improvement (though not significantly so in most cases) than the ginkgo-ginseng group. By contrast, when testing was at 2:30 p.m., the ginkgo-ginseng compound produced consistent memory benefits extending 2 weeks past the conclusion of treatment, with the only reversal being for picture recognition at 12 weeks. Moreover, in some cases the benefits were remarkable, with the ginkgo-ginseng group showing a 63% improvement at Week 14 relative to baseline for delayed word recall, compared with a 6% decrease for the placebo group.

These differences in the effects of ginkgo-ginseng across testing times are thus far unexplained, but they do suggest that the effects articulate with important dynamics of memory functioning. At the outset, we should note that the 7:30 a.m. testing was 1 hr before the daily dosage was administered, so that perhaps the just-mentioned patterns reflect an acute effect of the daily treatment dose. This explanation appears unlikely, however, because the pattern held at 14-week testing, 2 weeks after treatment was discontinued.

One alternative possibility hinges on circadian rhythms and memory functioning. As people age, memory (and cognitive) performance appears to become more influenced by preferred time of day. Older adults prefer early mornings, and they perform better on memory tests at their preferred time than at their nonpreferred time. Moreover, typical age-related memory decrements (with college students as the comparison group) are robust when memory is tested in the afternoon (older adults' nonpreferred time but college students' preferred time) but are attenuated or eliminated when memory is tested in the morning (older adults' preferred time but college students' nonpreferred time; Intons-Peterson, Rocchi, West, McLellan, & Hackney, 1999; May, Hasher, & Stoltzfus, 1993). The temporal pattern of the ginkgo-ginseng benefits reported by Wesnes et al. (2000) might thus be described as emerging primarily at later times in the day that are not optimal for upper-middle-aged adults' cognitive functioning. In line with this conjecture, Table 3 shows that at Week 0, performance was lower at 2:30 p.m. than 7:30 a.m. on every memory test in both groups. To the degree that nonpreferred times of day are associated with low cycles of biochemical or hormonal activity that may influence cerebral activation, these times may be precisely when agents that augment neural activity provide mnemonic benefits.

Another possibility is that by repeatedly testing lists of items throughout the testing day, Wesnes et al. (2000) created proactive interference (prior learning reducing subsequent learning of different items) for the later tests (e.g., Postman, 1962; Postman & Hasher, 1972). The last test of the day would be expected to suffer most from proactive interference, and it was

this test for which performance was worst. It was also this test that appeared to enjoy the most robust effects of the ginkgo-ginseng treatment. Maybe ginkgo-ginseng is especially helpful for memory situations with heavy interference. This possibility is consistent with the proposal that memory tasks that rely on frontal brain areas, areas thought to be most sensitive to aging (e.g., Raz, 2000; West, 1996), will be particularly likely to benefit from neuroprotective supplements. More specifically, with regard to the findings of Wesnes et al., proactive interference appears to be a particular problem in individuals with frontal dysfunction (Shimamura, Jurica, Mangels, & Gershberg, 1995). Our explanation of the ginkgo-ginseng findings in terms of preferred times of day or in terms of proactive interference is speculative, but does illustrate how more fine-grained considerations of aging and memory processes could help identify contexts in which candidate nutrients will most likely benefit memory, if they do so at all.

The frontal-dysfunction approach has been fruitfully applied to understanding the effects of aerobic exercise on memory. Kramer et al. (1999) evaluated the effects of 6-month regimens of aerobic (walking) or nonaerobic (stretching and toning) exercise on 15 tasks thought to vary in their reliance on the frontal lobes. Generally, they found selective benefits of aerobic exercise in components of tasks thought to be subserved by the prefrontal and frontal areas of the brain and no effects on other tasks.

Estrogen and Related Hormones

We provide a final concrete illustration, in the domain of hormone treatment and memory, of how a more analytic approach can be successful in exploring and delineating possible mnemonic effects of candidate supplements. Reduced estrogen levels accompany menopause, and postmenopausal women sometimes report difficulties with memory and concentration. Also, twice as many women as men are affected by Alzheimer's disease (Foy, Henderson, Berger, & Thompson, 2000). Accordingly, there has been much interest in the possibility that estrogen therapy after menopause (and hysterectomy) may improve memory and cognitive functioning and may provide some protective effects against Alzheimer's and other brain degenerative diseases. Some studies (not necessarily with placebo controls) have found that memory and cognitive performance are modestly better for women on estrogen therapy than for non-estrogen users, but other studies have found no improvement (Foy et al., 2000; for more extensive reviews, see Henderson, 2000, and LeBlanc, Janowsky, Chan, & Nelson, 2001).

A related hormone that has gained attention as a possible treatment for age-related declines in memory is *dehydroepiandrosterone* (DHEA; Hirshman et al., in press; Kalmijn et al., 1998; Wolf et al., 1997). This hormone is secreted by the adrenal cortex, and as people age, DHEA concentrations decrease significantly. DHEA may facilitate neural functioning in brain areas responsible for memory and may also have indirect effects on memory as a potential building block for estrogen (as well as testosterone) and as an agent that alleviates depression. At a general level, then, it is possible that DHEA treatments can improve memory in older adults, particularly in postmenopausal women.

A standard approach to testing such a possibility would be to select a known psychometric test to evaluate memory performance in placebo control groups and hormone-treated groups. Hirshman et al. (in press), however, adopted a more analytic approach. On the basis of preliminary work suggesting that increased DHEA enhances visual attention, Hirshman et al. reasoned that mnemonic effects of DHEA would be most likely for contexts in which visual presentation of target words is demanding. Accordingly, they manipulated the presentation time of the word lists subjects studied, so that presentation rates ranged from relatively fast paced to more moderately paced. Also, Hirshman et al. examined recognition memory performance, rather than recall, so that they could use signal detection analyses to extract values representing both accuracy and decision processes in recognition (see Swets, Dawes, & Monahan, 2000, in the inaugural issue of *Psychological Science in the Public Interest* for a recent monograph on application of signal detection theory to psychology). Postmenopausal women (ages 39–70) were given a 4-week daily oral dose of 50 mg of DHEA or placebo in a crossover (within-subjects) design.

As anticipated, DHEA improved recognition accuracy (relative to the placebo control) for short presentation durations (300 and 800 ms) but not for longer presentation durations (over a second). Further, DHEA produced substantially and significantly more conservative decision criteria (subjects had to feel more confident that an item was on the list before they were willing to endorse it as a target item) than the control treatment. Because more conservative decision criteria are associated with strong memory experiences, Hirshman et al. (in press) argued that DHEA is effective in strengthening memory experiences for perceptually brief (visual) events. By using theoretically motivated manipulations and memory tests, Hirshman et al. were able to begin to delineate the conditions for and possible underpinnings of the mnemonic effects for DHEA.

SUMMARY AND CONCLUDING REMARKS

With improvements in medical technology as well as personal health habits, more people are living longer. Because memory loss accompanies normal aging and many pathological conditions are associated with aging, it is important to examine whether there are nutrients (nootropic-like substances) that can slow down or even reverse memory loss. Currently, there is strong interest among older adults for over-the-counter "brain boosters," and many of these are marketed with grand claims touting their benefits. The purpose of this review was to examine whether these claims hold up to scientific scrutiny.

There are sound biochemical reasons for expecting the nutrients we have discussed to be effective; for the most part,

their effects tend to be fairly robust in the animal studies, and there are occasionally impressive results with humans. Nonetheless, there are questions about sample size, the generality of the results across different memory tests and populations, and other aspects of the procedures and data. These problems, in conjunction with a general lack of research demonstrating that the effects can be replicated, dampen enthusiasm for the effectiveness of these nutrients in substantially arresting or reversing memory loss. All in all, we believe that the current data do not allow strong scientifically based recommendations for any of these memory nutrients.

However, the data also do not allow us to conclude that these nutrients are ineffective in boosting memory. Like Gold et al. (this issue), we believe that there are enough positive results with at least some of these nutrients to suggest that this is an important area for further research.

We have several recommendations for future research, beyond the obvious fact that the reliability of existing findings needs to be determined. One is that more research should be conducted with healthy older adults. Most of the tests of these nutrients have been conducted with humans who have various pathological conditions associated with aging, and some of these nutrients may have their greatest effects in brains that are on the decline but not to the point that dementia is clinically present (cf. Crook et al., 1991; Spiers et al., 1996). That is, the benefits of some of these nutrients may not be realized in brains that have undergone substantial damage. It may also be important to study the effects of these nutrients in middle age, when the first signs of age-associated memory declines appear.

Our second recommendation is that researchers develop a more analytical approach to determining the benefits of these nutrients on specific memory processes (along the lines of the research of Hirshman et al., in press, and Kramer et al., 1999). Specifically, it may be that different nutrients create benefits for different kinds of memory processes. For example, it may be that agents that are thought to have effects on the structural integrity of neurons (e.g., PS) may have greater effects on storage processes, whereas nutrients that are thought to boost the energy production of neurons (e.g., ALC) may have greater effects on more effortful memorial processes such as tasks requiring deep processing (McDaniel, Einstein, & Lollis, 1988; Tyler, Hertel, McCallum, & Ellis, 1979) or possibly self-initiated retrieval (Craik, 1986).

A third recommendation emanates from the realization that aging is a highly complex process that has numerous effects on the brain. Thus, individual nutrients alone may do little to offset the many cascading effects of aging, and a rationally derived combination of nutrients (e.g., the ginkgo-ginseng combination used by Wesnes et al., 2000; Schiffer, 1999, has suggested a vinpocetine-ALC combination) may be more promising. We hope that the tantalizing effects of these nutrients revealed in the existing literature will stimulate a more focused and analytic effort to enhance understanding of their mnemonic benefits (or lack thereof).

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