

# Enhancement of Memory in Alzheimer Disease With Insulin and Somatostatin, but Not Glucose

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**Background:** Increasing plasma glucose levels improves memory in patients with Alzheimer disease (AD). Increasing plasma glucose levels also increases endogenous insulin levels, raising the question of whether memory improvement is due to changes in insulin, independent of hyperglycemia. We address this question by examining memory and counterregulatory hormone response during hyperglycemia when endogenous insulin was suppressed by concomitant infusion of the somatostatin analogue octreotide (Sandostatin).

**Methods:** Twenty-three patients with AD and 14 similarly aged healthy adults participated in 4 metabolic conditions on separate days: (1) hyperinsulinemia (538 pmol/L) with fasting glucose (5.6 mmol/L [100 mg/dL]), achieved by insulin and variable dextrose infusion; (2) hyperglycemia (12.5 mmol/L [225 mg/dL]) with fasting insulin (57 pmol/L), achieved by dextrose and somatostatin (octreotide) infusion (150 mg/h); (3) placebo with isotonic sodium chloride solution (saline) infusion (fasting insulin and glucose); and (4) an active control condition in which somatostatin alone was infused

(150 mg/h). Declarative memory (story recall) and selective attention (Stroop interference test) were measured during steady metabolic states.

**Results:** Patients with AD showed improved memory during hyperinsulinemia relative to placebo ( $P = .05$ ) and relative to hyperglycemia ( $P < .005$ ). Memory did not improve during hyperglycemia when insulin was suppressed. Somatostatin analogue infusion alone also improved memory for patients with AD ( $P < .05$ ). Hyperinsulinemia increased cortisol levels in subjects with AD, whereas somatostatin alone lowered cortisol concentrations.

**Conclusions:** These results confirm that elevated insulin without hyperglycemia enhances memory in adults with AD, and indicate that insulin is essential for hyperglycemic memory facilitation. These results also suggest a potential therapeutic role for somatostatin in AD.

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**A**LZHEIMER disease (AD) is accompanied by disrupted glucose metabolism and insulin resistance that may contribute to its characteristic memory impairment.<sup>1-3</sup> Increasing glucose availability by raising plasma glucose levels improves memory for new information in patients with AD.<sup>2,4-6</sup> Such memory facilitation is associated with a glucose-stimulated elevation in endogenous insulin levels, raising the question of whether improvement is due to changes in insulin, independent of hyperglycemia. In previous work, we have demonstrated that raising insulin levels while keeping plasma glucose at fasting baseline levels was sufficient to improve memory for patients with AD.<sup>2</sup> However, the question remains whether raising plasma glucose levels alone without an accompanying elevation in in-

sulin is also sufficient to enhance memory. This question is of considerable theoretical import. Although numerous studies have demonstrated that raising plasma glucose to an optimal level improves memory for healthy adults and patients with AD,<sup>7</sup> insulin effects on cognitive abilities such as memory have only been recently demonstrated.<sup>2</sup> Indeed, the question of whether and how the brain is affected by insulin is controversial. A potential role for insulin in the brain is supported by documentation of dense insulin receptor distributions in several brain regions, including the CA1, CA3, and dentate gyrus regions of the hippocampus, entorhinal cortex, hypothalamus, and olfactory bulb.<sup>8,9</sup> Interestingly, these regions are also affected earliest and most severely in patients with AD.

The finding that hyperglycemic memory facilitation is abolished when

## SUBJECTS AND METHODS

### SUBJECTS

This study was approved by the Human Subjects Committee of the University of Washington, Seattle. Written informed consent was obtained from all subjects and from the legal representatives of the patients with AD. Subjects were 23 patients with AD and 14 healthy adults recruited from the Clinical Core of the University of Washington Alzheimer's Disease Research Center. All subjects received \$100 for their participation in the study. Subjects with AD and healthy subjects did not differ with respect to age, education, body mass index, or fasting plasma glucose level (**Table 1**). All subjects were in good physical health with stable weights for at least 2 months. Subjects were screened by medical history, physical examination, and by evaluation of serum electrolytes, glucose, renal, thyroid and hepatic function, and complete blood cell count. Subjects were free from past or present psychiatric disorders, alcoholism, head trauma, uncontrolled hypertension, neurologic disorders other than AD, diabetes mellitus, chronic obstructive pulmonary disease, congestive heart failure, or cardiac arrhythmias. No subjects were taking medication with cognition-enhancing or other known central nervous system effects, or that affected glucose regulation. The AD subjects met National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association criteria for probable AD as determined by board-certified neurologists and psychiatrists in the Clinical Core,<sup>15</sup> were community-dwelling, and at mild-to-moderate stages of the disease. Dementia Rating Scale<sup>16</sup> scores and other clinical data are presented in Table 1.

### INFUSION PROTOCOL

All healthy subjects and 19 of 23 AD subjects participated in 3 metabolic conditions on separate days at least 1 week apart but not more than 6 weeks apart: (1) *Hyperinsulinemia with basal (fasting) plasma glucose*. As described by Craft et al,<sup>2</sup> subjects were maintained at plasma insulin levels of about 538 pmol/L using an insulin infusion dose of 1.0 mU · kg<sup>-1</sup> · min<sup>-1</sup>. Dextrose (20%) was infused as needed to keep plasma glucose at levels of about 5.6 mmol/L (100 mg/dL). (2) *Hyperglycemia with basal (fasting) plasma insulin*. Dextrose was infused to reach and maintain glucose plasma levels of 12.5 mmol/L (225 mg/dL) while a somatostatin analogue (octreotide; Sandostatin, Sandoz Pharmaceuticals, Hanover, NJ) was infused at a rate of 150 mg/h to suppress the endogenous insulin response. (3) *Placebo*. Both plasma glucose and insulin were maintained at fasting levels (insulin levels of about 57 pmol/L and glucose levels of about 5.6 mmol/L [100 mg/dL]) with saline infusion. A subset of subjects also participated in a fourth, active control condition: (4) *Somatostatin with basal glucose and insulin*. Octreotide was infused at a rate of 150 mg/h while both plasma glucose and insulin were maintained at fasting baseline levels. Six healthy subjects and 12 AD subjects participated in the fourth condition; 8 of the AD subjects also participated in the first 3 conditions, whereas 4 AD subjects only participated in the placebo and somatostatin conditions owing to time constraints. Order of all conditions was counterbalanced, and subjects and testers were blinded to condition. Plasma glucose and insulin levels were similar between AD and healthy groups in all

conditions (**Table 2** and **Table 3**). Insulin values in the hyperglycemic and somatostatin-alone condition did not differ statistically from the placebo condition. Glucose values did not differ between placebo, hyperinsulinemic, and somatostatin-alone conditions.

Subjects rested with intravenous lines in place for a 30-minute habituation period. Dextrose, insulin, somatostatin, or saline were then infused until target levels were reached (approximately 90 minutes), after which a 30-minute stabilization period occurred. Following this stabilization period, a 30-minute cognitive protocol was administered, and 3 blood samples were obtained through an indwelling catheter at 0, 15, and 30 minutes during the protocol. Plasma glucose was measured at 5- to 10-minute intervals throughout each session with a glucose oxidase method (Beckman Glucose Analyzer, Fullerton, Calif). Plasma insulin, cortisol, corticotropin, epinephrine, and norepinephrine were measured with radioenzymatic assays or radioimmunoassays.<sup>2</sup> Values for the 3 samples obtained during each cognitive protocol were averaged to ensure a reliable measure.

### COGNITIVE TESTING

Four comparable versions of the cognitive protocol were assigned in counterbalanced order to the 4 metabolic conditions. Each protocol included a declarative memory and a selective attention measure. The latter measure was included to determine whether metabolic effects were limited to memory. Story recall was selected as the primary memory measure because it is a sensitive indicator of memory loss in early AD,<sup>17</sup> and has been widely used in previous studies of hyperglycemic memory facilitation.<sup>2,4,5</sup> Subjects heard a brief narrative containing 44 informational bits, and were asked to recall as much as possible both immediately and after a 10-minute delay. Subjects received credit for each informational bit recalled verbatim or for accurate paraphrases. Immediate and delayed scores were summed.

The Stroop Color-Word Interference selective attention task had 3 conditions.<sup>18</sup> In the first 2 conditions, subjects were asked to read color words, and to name colors. In the interference condition, subjects were required to name the ink color of color names printed in discordant colors (eg, the word "red" printed in blue). Subjects were thus required to selectively attend to the color of the word and inhibit the prepotent reading response. Completion time and number of errors were recorded.

### STATISTICAL ANALYSIS

For AD and healthy groups, cognitive scores were log transformed and subjected to repeated-measures analysis of variance (ANOVA) with condition (placebo, hyperinsulinemia, hyperglycemia) as the within-subjects factor. Effects with  $P < .05$  were considered statistically significant, and all significance tests were 2 tailed. Following a significant F for condition, planned contrasts were conducted comparing performance in the hyperinsulinemic condition and in the hyperglycemic condition to performance in the placebo condition. Repeated-measures ANOVA was also used to compare cognitive scores in the placebo and somatostatin conditions for subjects who participated in these conditions. Repeated-measures ANOVA was conducted with hormone values, with Bonferroni post hoc tests used to determine the direction of significant effects.

## COGNITIVE MEASURES

insulin is suppressed would suggest that previous observations of enhanced memory with glucose administration are not due to glucose per se, but instead due to changes in endogenous insulin levels in response to elevated glucose. This finding would also support previous studies suggesting that defects in insulin action may contribute to the pathophysiology of AD, and to its characteristic memory impairment.<sup>2,10</sup> One method of suppressing endogenous insulin during hyperglycemia is by administering the neuropeptide somatostatin, which inhibits insulin release from pancreatic beta cells.<sup>11</sup> Somatostatin levels and receptor distributions are consistently noted to be reduced in AD,<sup>12-14</sup> although the significance of this observation has not been established.

The present study measured memory and attention in patients with AD and healthy adults in 4 conditions: (1) when plasma insulin was raised to levels that previously facilitated performance while glucose was maintained at a fasting level; (2) when plasma glucose was raised to levels that previously facilitated memory while keeping insulin at a fasting level by concomitant administration of somatostatin; (3) when fasting levels of insulin and glucose were maintained with isotonic sodium chloride solution (saline) infusion; and (4) an active control condition, in which somatostatin was administered alone while glucose and insulin remained at fasting levels. The inclusion of this condition was necessary to determine whether the failure to observe memory facilitation during hyperglycemia was due to an inhibitory effect of somatostatin, rather than the absence of insulin. In addition, in light of the well-documented somatostatinergic deficiency in AD, it is possible that somatostatin might exhibit independent effects on memory. Given previous findings that insulin-induced memory improvement was accompanied by changes in neuroendocrine counterregulation, plasma cortisol, corticotropin, epinephrine, and norepinephrine levels were measured during each condition.<sup>2</sup> Finally, we included a comparison group of similarly aged healthy adults to determine whether their memory and counterregulatory responses differed from patients with AD, an observation that might have pathogenetic implications.

Memory performance was greater in the hyperinsulinemic condition than in the placebo or the hyperglycemic condition for the AD group, whereas no difference in memory performance was observed between the placebo and hyperglycemic conditions (**Figure 1**). The repeated-measures ANOVA showed a significant overall effect of condition ( $F_{2,17} = 5.79, P = .02$ ). Planned contrasts documented better performance during hyperinsulinemia relative to placebo ( $F_{1,18} = 4.70, P = .05$ ) and relative to hyperglycemia ( $F_{1,18} = 10.26, P < .005$ ). No differences were

**Table 1. Clinical and Demographic Data for AD and Healthy Subjects\***

	AD Group (n = 23)	Healthy Group (n = 14)
Age, mean (SD), y	70.5 (10.6)	69.2 (8.0)
Education, mean (SD), y	14.8 (2.5)	16.0 (2.5)
Sex, M/F	12/11	7/7
Race, No.		
White	22	13
Black	1	1
BMI, mean (SD), kg/m <sup>2</sup>	25.1 (2.5)	24.0 (2.2)
Fasting glucose, mean (SD), mmol/L [mg/dL]	5.9 (0.8) [106 (14)]	5.5 (0.4) [99 (7)]
DRS score, mean (SD)	112.7 (16.4)	137.9 (12.9)
Age at AD diagnosis, mean (SD), y	69.9 (10.6)	...
Duration of AD, mean (SD), mo	11.4 (13.8)	...
Medications, No. (%) of subjects		
Multivitamins	11 (48)	6 (43)
Aspirin/NSAIDs	4 (17)	2 (14)
Hormone replacement therapy	4 (17)	3 (21)
Thyroid hormone	3 (13)	2 (14)
ACE inhibitors	2 (9)	0
Calcium channel blockers	1 (4)	1 (8)
Cholesterol-lowering agents	1 (4)	0
β-Blockers	1 (4)	3 (21)
Gastric acid inhibitors	1 (4)	1 (8)

\*AD indicates Alzheimer disease; BMI, body mass index; DRS, Dementia Rating Scale; ellipses, data not computed; NSAIDs, nonsteroidal anti-inflammatory drugs; and ACE, angiotensin-converting enzyme.

**Table 2. Plasma Concentrations for AD and Healthy Subjects During the Placebo, Hyperglycemic, and Hyperinsulinemic Conditions\***

Neuroendocrine Measure	Healthy Group (n = 14)			AD Group (n = 19)		
	Placebo	Hyperglycemia	Hyperinsulinemia	Placebo	Hyperglycemia	Hyperinsulinemia
Glucose, mmol/L	5.4 (0.6)	13.0 (0.8)	5.9 (0.4)	5.4 (0.6)	13.0 (0.8)	5.7 (0.3)
Insulin, pmol/L	62 (17)	54 (2)	559 (103)	61 (19)	58 (23)	544 (133)
Cortisol, nmol/L†	107.0 (40.3)	97.1 (55.2)	154.0 (46.1)	196.7 (44.1)	171.6 (73.7)	237.5 (61.2)
Corticotropin, pmol/L‡	3.0 (1.3)	1.7 (0.7)	2.8 (1.4)	3.1 (1.4)	2.9 (1.6)	3.9 (2.2)
Norepinephrine, nmol/L§	1914 (590)	1832 (763)	2436 (1040)	2458 (1632)	2115 (949)	2669 (1332)
Epinephrine, pmol/L	342 (179)	249 (171)	346 (205)	324 (192)	231 (161)	344 (214)

\*Data are given as mean (SD). AD indicates Alzheimer disease. To convert glucose to milligrams per deciliter, divide by 0.05551.

†Cortisol levels were significantly higher for AD group in all conditions. The AD group had higher cortisol levels during the hyperinsulinemic condition compared with placebo.

‡Corticotropin levels were significantly lower during the hyperinsulinemic condition compared with placebo for the healthy group.

§Norepinephrine levels were significantly higher during the hyperinsulinemic condition compared with placebo for the healthy group.

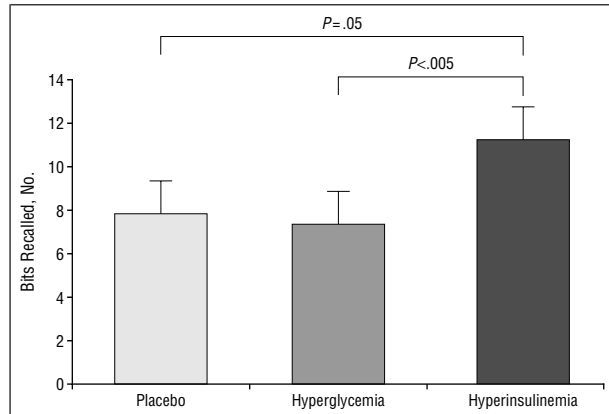
||Epinephrine levels were significantly lower during the hyperglycemic condition compared with placebo for both groups.

**Table 3. Plasma Concentrations for AD and Healthy Subjects During the Placebo and Somatostatin Conditions\***

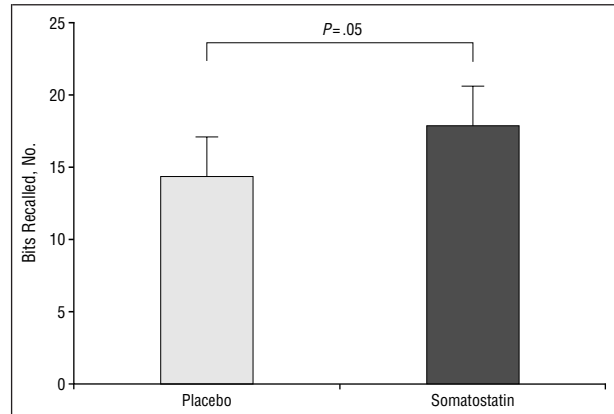
Neuroendocrine Measure	Healthy Group (n = 6)		AD Group (n = 12)	
	Placebo	Somatostatin	Placebo	Somatostatin
Glucose, mmol/L	5.9 (0.5)	5.9 (1.0)	5.5 (0.7)	6.0 (1.0)
Insulin, pmol/L	59 (14)	30 (6)	79 (51)	29 (6)
Cortisol, nmol/L†	229.0 (78.1)	148.7 (87.7)	208.3 (53.8)	161.4 (46.9)
Corticotropin, pmol/L†	4.0 (1.5)	1.9 (1.2)	4.2 (1.9)	2.3 (1.6)
Norepinephrine, nmol/L	1543 (402)	1589 (290)	2093 (902)	1722 (636)
Epinephrine, pmol/L†	167 (85)	118 (71)	223 (89)	122 (60)

\*Data are given as mean (SD). AD indicates Alzheimer disease. To convert glucose to milligrams per deciliter, divide by 0.05551.

†Cortisol, corticotropin, and epinephrine levels were significantly lower with somatostatin than with placebo for both groups.



**Figure 1.** Story recall (means with SEs) during the placebo, hyperglycemic, and hyperinsulinemic conditions for subjects with Alzheimer disease ( $n = 19$ ). Recall was greater during hyperinsulinemia than during placebo ( $F_{1,18} = 4.70$ ,  $P = .05$ ) or hyperglycemia ( $F_{1,18} = 10.26$ ;  $P < .005$ ). Recall during the placebo and hyperglycemic conditions did not differ.



**Figure 2.** Story recall (means with SEs) during placebo and somatostatin infusion for subjects with Alzheimer disease ( $n = 12$ ). Recall was greater with somatostatin than with placebo ( $F_{1,11} = 4.97$ ,  $P = .05$ ).

observed between hyperglycemic and placebo conditions ( $F_{1,18} = 0.74$ ,  $P = .42$ ). Hyperinsulinemic enhancement was selective for story recall; no effect of condition was observed for the Stroop task ( $F_{2,15} = 1.69$ ,  $P = .22$ ).

Interestingly, subjects with AD showed a significant degree of memory improvement in story recall in the somatostatin condition relative to the placebo condition ( $F_{1,11} = 4.97$ ,  $P = .05$ ) (**Figure 2**). Effect sizes calculated according to Cohen<sup>19</sup> for comparisons between placebo and hyperinsulinemic conditions, and placebo and somatostatin conditions, were moderate to large (effect size = 0.27 and 0.45, respectively). No change was observed in performance on the memory or selective attention test for healthy subjects in any condition (**Table 4**), which may reflect a different dose-response curve for healthy adults than for AD patients.

#### NEUROENDOCRINE MEASURES

Neuroendocrine data are presented in Tables 2 and 3. The AD group had higher cortisol levels than the healthy group in each of the 3 conditions ( $F_{1,16} = 18.78$ ,  $P < .001$ ;  $F_{1,16} = 9.51$ ,  $P < .008$ ; and  $F_{1,16} = 5.22$ ,  $P = .04$ , for the placebo, hyperinsulinemic, and hyperglycemic conditions, respectively). The AD group had higher cortisol levels in the hyperinsulinemic condition relative to

the placebo condition ( $F_{1,16} = 8.42$ ,  $P = .02$ ). In contrast, no differences were observed between AD and healthy groups for corticotropin. Healthy subjects had lower corticotropin values in the hyperglycemic condition relative to the placebo condition ( $F_{1,6} = 18.82$ ,  $P < .005$ ). Both AD and healthy subjects had significantly lower cortisol levels during somatostatin infusion relative to saline infusion, resulting in a significant effect for condition ( $F_{2,26} = 9.49$ ,  $P < .001$ ). A similar lowering of corticotropin levels was observed for all subjects during somatostatin infusion ( $F_{1,9} = 28.84$ ,  $P < .001$ ).

No differences were observed between AD and healthy groups for epinephrine or norepinephrine in any of the 3 conditions. For AD and healthy groups, epinephrine levels were reduced in the hyperglycemic condition relative to the placebo condition ( $F_{1,16} = 6.24$ ,  $P = .03$  and  $F_{1,13} = 34.69$ ,  $P < .001$  for the AD and healthy groups, respectively), whereas no differences were observed between the placebo and hyperinsulinemic conditions. The healthy group had higher norepinephrine values in the hyperinsulinemic condition than in the placebo condition ( $F_{1,13} = 4.86$ ,  $P < .05$ ). No changes were observed in norepinephrine levels from placebo to somatostatin conditions for AD or healthy groups. Epinephrine levels decreased during somatostatin infusion relative to placebo infusion for both groups ( $F_{1,14} = 15.98$ ,  $P < .001$ ).



**Table 4. Story Recall and Stroop Scores for Healthy Subjects by Condition\***

	All Subjects (n = 14)			Subject Subset (n = 6)	
	Placebo	Hyperglycemia	Hyperinsulinemia	Placebo	Somatostatin
Story recall, No. of bits recalled	41.7 (15.1)	38.1 (8.6)	43.4 (13.0)	42.9 (15.8)	42.0 (16.5)
Stroop time, s	47.6 (8.7)	50.0 (7.4)	51.9 (13.1)	46.3 (8.1)	54.5 (14.7)
Stroop errors, No.	0.1 (0.4)	0.1 (0.4)	0.1 (0.4)	0.2 (0.4)	0.0 (0.0)

\*Data are given as mean (SD).

### COMMENT

Declarative memory was selectively improved during hyperinsulinemia for adults with AD. In contrast, memory was unchanged in the hyperglycemic condition, in which plasma glucose was raised to levels that were associated with memory enhancement in 4 prior studies.<sup>2,4-6</sup> Unlike these previous investigations, however, in the present study the endogenous insulin response to hyperglycemia was suppressed. The failure to find memory facilitation in the hyperglycemic condition cannot be attributed to inhibitory effects of somatostatin, the neuropeptide used to suppress insulin in this condition. On the contrary, somatostatin infusion during euglycemia resulted in significant memory facilitation for patients with AD. Taken together, these results suggest that insulin and insulin-associated mechanisms are essential for hyperglycemic memory enhancement in patients with AD. Moreover, previously reported glucose-induced memory improvement for patients with AD is likely secondary to elevations in endogenous insulin in response to hyperglycemia.

The present results suggest that insulin affects the medial temporal declarative memory system, although the precise mechanisms through which such effects occur must remain speculative. Dense insulin receptor distributions have been documented in the dentate gyrus, CA1, and CA3 fields of the hippocampus.<sup>8,9,20</sup> These regions are known to play a role in declarative memory and are among the regions affected earliest and most severely by the neuropathologic changes of AD.<sup>21</sup> Raising plasma insulin levels results in increased insulin binding in hippocampus, demonstrating that changes in peripheral insulin levels can affect the brain.<sup>20</sup> In turn, increasing brain insulin levels results in increased glucose utilization in the entorhinal cortex.<sup>22</sup> Recent observations that the insulin-sensitive glucose transporter GLUT4 is present in the hippocampus provide a mechanism for direct insulin effects on brain glucose metabolism,<sup>23</sup> and argue against the traditional notion that the brain is not an insulin-sensitive organ. Insulin-promoted increases in glucose utilization also result in glycolytic production of acetyl-CoA and corresponding increases in acetylcholine,<sup>24</sup> a neurotransmitter closely linked to memory function and severely reduced in AD.

In the present study, the somatostatin analogue octreotide facilitated memory at basal glucose levels for patients with AD. Somatostatin is a neuropeptide with 5 known receptor types (somatostatin receptor types [SSRT] 1-5) in human brain.<sup>25</sup> In particular, SSRT2 receptors, the primary target of the somatostatin analogue octreotide used

in the present study,<sup>26</sup> have been observed in the pyramidal layer of CA1, the granule cell layer of the dentate gyrus, the subiculum, and entorhinal cortex, as well as in frontal lobe.<sup>25</sup> Recent studies have demonstrated that SSRT2 receptors are selectively reduced in frontal cortex and hippocampus of patients with AD.<sup>12,14</sup> Administration of octreotide improves memory and increases hippocampal cholinergic activity in rodents, and enhances long-term potentiation.<sup>27-30</sup> Such findings represent a potential basis for the memory enhancement observed in patients with AD following octreotide administration. However, evidence suggests that octreotide does not readily cross the blood-brain barrier.<sup>31</sup> Thus, further work is needed to determine whether the memory enhancement observed following intravenous somatostatin administration in the present study reflects indirect effects of somatostatin, or compromised blood-brain barrier integrity in AD. Further study is also needed to identify the mechanisms through which hyperglycemia abolished the facilitatory effects of somatostatin. Similarly, the relationship between the memory-facilitating mechanisms induced by somatostatin and insulin is unclear. As intended, somatostatin administration suppressed plasma insulin, and thus memory facilitation in this condition must have occurred by an insulin-independent mechanism.

Two previous reports<sup>32,33</sup> have investigated the therapeutic efficacy of somatostatin analogues in AD, both of which reported negative findings. The use of different somatostatin analogues, small sample sizes, lower doses, and diversified administration protocols may account for the different pattern of results. Based on the negative findings of their study, Mouradian et al<sup>33</sup> concluded that "stimulation of the somatostatin system has no value in the symptomatic treatment of Alzheimer dementia."<sup>33</sup> The present results contradict that conclusion, and suggest that further investigation of octreotide and other SSRT2-selective somatostatin analogues as potential therapeutic agents in AD is warranted.

In the present study, insulin and somatostatin administration were associated with changes in cortisol levels. The AD group had increased cortisol levels during hyperinsulinemia, the condition in which memory improvement was observed. This observation is somewhat puzzling, because several investigators have demonstrated that increased cortisol is associated with memory decline.<sup>34,35</sup> In contrast, hyperinsulinemia was not associated with increased corticotropin levels in the AD or healthy group. The finding that patients with AD have higher cortisol levels than healthy adults despite similar corticotropin levels has been interpreted as indicating greater responsiveness to corticotropin in AD.<sup>36</sup> Consis-

tent with previous investigations, somatostatin administration was associated with reduced cortisol, corticotropin, and epinephrine levels for both healthy and AD groups.<sup>37-39</sup> The cause and significance of such effects are not clear at this time.

In summary, defects in insulin-mediated energy metabolism have been linked to the pathophysiology and memory impairment of AD. The present results provide additional support for this relationship by demonstrating that insulin is essential for memory enhancement previously thought to result primarily from increasing glucose availability. The present study also demonstrates a potential therapeutic role for somatostatin in AD. Determining the precise mechanisms through which insulin and somatostatin facilitate memory is of critical importance, as this knowledge may identify pathogenetic factors in AD, as well provide new insight into insulin's role in normal memory function.

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## CONCLUSIONS

Our data indicate that depressed patients in clinical trials who are assigned to placebo treatment are not at greater risk for suicide or suicide attempts than those assigned to active treatment. Depressed patients who are assigned to placebo experience substantial symptom reduction. We hope that these and other pertinent data can usefully inform deliberations about the risks, benefits, and ethics of placebo-controlled antidepressant studies.

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## Correction

**Typographical Errors in Drug Dosage Units.** In the article by Craft et al titled "Enhancement of Memory in Alzheimer Disease With Insulin and Somatostatin, but Not Glucose," published in the December 1999 issue of the ARCHIVES (1999;56: 1135-1140), typographical errors appear in the dosage unit for octreotide. On page 1135, lines 8 and 12 of the "Methods" heading of the abstract, and on page 1136, lines 13 and 20 of the "Infusion Protocol" subsection of the "Subjects and Methods" section, the unit following 150 should have read "µg/h" (micrograms per hour).