Pharmacology Biochemistry and Behavior, Vol. 58, No. 1, pp. 209–214, 1997
© 1997 Elsevier Science Inc.
Printed in the USA. All rights reserved
0091-3057/97 $17.00 + .00

ELSEVIER

PII S0091-3057(97)00064-6

Effect of Combinations of Insulin, Glucose and Scopolamine on Radial Arm Maze Performance

JEFF G. BLANCHARD AND PERRY M. DUNCAN[1]

Department of Psychology, Old Dominion University, Norfolk, VA 23529-0267

Received 25 April 1996; Revised 21 October 1996; Accepted 21 October 1996

BLANCHARD, J. G., AND P. M. DUNCAN. *Effect of combinations of insulin, glucose and scopolamine on radial arm maze performance.* PHARMACOL BIOCHEM BEHAV **58**(1) 209–214, 1997.—Previous research has shown that glucose is an effective agent in facilitating memory performance and in attenuating scopolamine-induced amnesia. Although insulin has not been shown to facilitate unimpaired memory, a previous study has demonstrated that insulin can also attenuate scopolamine-degraded memory. The present study was designed to determine how different combinations of insulin, glucose and scopolamine affect memory. It involved nine rats whose memory was assessed through performance in a win-shift radial arm maze task under different drug treatments. A 2 × 2 × 2 (insulin × glucose × scopolamine) within-subjects design with a 5-h drug test interval was employed. Scopolamine disrupted memory performance, and both glucose and insulin counteracted this disruption. Combining the glucose and insulin treatments did not increase their ability to attenuate scopolamine deficits but slightly decreased this effect. Glucose tended to enhance memory, even in the absence of scopolamine, whereas insulin had no effect on memory in the absence of scopolamine. Blood glucose levels were measured and did not indicate changes caused by drug treatments. The memory effects may have been due to the acetylcholine-agonist actions of glucose and insulin, an interpretation consistent with previous research findings. © 1997 Elsevier Science Inc.

Insulin Glucose Scopolamine Radial arm maze Win-shift Memory Blood glucose

PREVIOUS research has shown that several pharmacological agents can either facilitate or impair memory function. Scopolamine, an acetylcholine antagonist, is a drug that impairs performance on memory tasks (3). That scopolamine both acts as an acetylcholine antagonist and interrupts memory performance is consistent with other research demonstrating that memory processes are modulated by a cholinergic system (14).

A continuous supply of glucose is critical for normal brain function, and administration of additional glucose can sometimes improve memory performance. This memory facilitation by glucose is dose dependent, with a dose of 100 mg/kg being most effective for both human and animal subjects (15,28,37). Although several proposals have been made (16), the exact mechanism through which glucose affects memory is not clearly understood. One possibility is that glucose acts as an acetylcholine agonist. Consistent with this proposal, one study (25) has demonstrated that glucose can attenuate the amnesia produced by scopolamine while reducing the increase in high affinity choline uptake during conditions of high acetylcholine demand. These investigators proposed that glucose may increase the availability of acetyl coenzyme A, which is necessary in the synthesis of acetylcholine (40). Another study showed that glucose augmented rapid eye movement sleep (which depends on cholinergic function) in old rats (35).

Some investigators (11,12,16,32) have proposed that a diminution in glucose utilization resulting from dysfunctional glucose metabolism/regulation may contribute to the cognitive deficits found in Alzheimer patients. Because insulin promotes glucose utilization, particularly in muscle cells, the possibility of insulin regulating cognitive/memory function warrants investigation. Indirect evidence that insulin may be associated with memory impairment among diabetic and Alzheimer patients comes from many clinical observations (26).

One study (11) demonstrated that, in the later stages of Alzheimer disease, insulin levels are low and that glucose injections have no alleviating effect on memory impairment, unlike in earlier stages when insulin levels are high and glucose injections facilitate memory performance. The memory impairment found among late-stage Alzheimer patients in this study may have been due to an inability to utilize glucose, in

[1]To whom requests for reprints should be addressed. E-mail: pmd200f@viper.mgb.odu.edu

turn caused by poor insulin regulation. However, the results of many such studies investigating blood glucose regulation in Alzheimer patients appear to be rather inconsistent (26).

Whether insulin can regulate glucose metabolism within the brain has been a controversy for some time. Baskin et al. (2) summarized data that challenge the traditional view that insulin is not involved in such brain glucose regulation. The conflicting nature of the results from studies investigating the role of insulin in the brain may be due in part to the characteristics of the brain insulin system.

The brain synthesizes insulin, and insulin receptor sites are located in structures such as the hippocampus that are implicated in memory (4,23). Furthermore, there appear to be at least two types of insulin receptors in the brain—one found on neuronal cells and the other on glial cells. Glial-type insulin receptors can facilitate glucose utilization in the presence of increased insulin levels, whereas neuronal-type receptors have direct effects on neural function without affecting glucose metabolism. Because baseline utilization of glucose in neurons is much greater than that of glial cells, any increase in glucose utilization by glial cells in the presence of increased insulin levels may have gone unnoticed in previous studies (4).

Because there are two types of insulin receptors found in the brain, insulin may be implicated in memory processes through two routes: a glucose-dependent route and a glucose-independent route. The glucose-independent route would involve neuronal insulin receptors that have direct effects on the central nervous system (CNS). Other investigators (24) have made a similar suggestion, based on the observation that insulin (0.8 IU/kg) attenuates scopolamine-produced amnesia of mice in a bar-pressing task. With regard to the possible CNS effects underlying insulin's improvement of memory performance, these investigators proposed that insulin may directly facilitate acetylcholine activity. Consistent with their hypothesis, they noted that a previous study (21) demonstrated that in cultured neurons insulin stimulates the activity of choline acetyltransferase, an enzyme that catalyzes the synthesis of acetylcholine (7).

Because both glucose and insulin may act as acetylcholine agonists, administering a combination of these could yield an additive effect in attenuating scopolamine-induced amnesia. In addition, combining insulin with glucose may allow for greater utilization of glucose and, as a consequence, greater ability to compensate for scopolamine-induced amnesia. The latter proposal is consistent with observations (30,36) that scopolamine can impair glucose uptake and utilization.

In a study of the conditioned emotional responses of male rats, the effect of combined insulin and glucose injections on memory retention was investigated (27). This combination of treatments interacted, allowing higher (4 g/kg) doses of glucose to facilitate memory to an extent approximately equal to that of an intermediate (2 g/kg) dose. A wide dose range (0.25–4 IU/kg) of insulin injections alone failed to affect memory retention in either direction (27). That combined insulin and glucose administrations did not significantly improve memory to a greater extent than glucose alone and that insulin alone failed to affect memory may have been due to the lack of any memory-impairing treatments in this experiment (i.e., impaired glucose utilization or decreased acetylcholine activity).

The purpose of the present study was to determine whether insulin and glucose administered simultaneously could attenuate scopolamine-induced amnesia to a greater degree than either insulin or glucose alone. We hypothesized that this combination should permit greater memory facilitation because both substances act as acetylcholine agonists. In addition, by preventing insulin-induced hypoglycemia, this combination may allow for the determination of whether the insulin attenuation of scopolamine-induced amnesia found in the Messier and Destrade study (24) was due to a possible hypoglycemic counterregulatory release of epinephrine, a substance widely implicated in the modulation of memory (8–10, 13,18,34,37,38).

The radial arm maze has become a widely used paradigm for investigation of memory in rodents. An additional purpose of the present experiment was to determine whether the scopolamine–insulin interaction would generalize to the radial arm maze. Therefore, in measuring rat's memory retention under different conditions, the present experiment used a win-shift eight-arm radial maze task. An earlier study has shown the utility of this task in demonstrating glucose modulation of memory (28).

With a $2 \times 2 \times 2$ within-subjects factorial design, the present experiment tested memory retention of rats as a function of treatment with different combinations of insulin, glucose, scopolamine and/or saline. Drug injections were administered at the beginning of a 5-h delay between an acquisition trial and a test trial. An effort was made to use doses comparable to those of previous studies and to use a dose of insulin and scopolamine that would not result in behavioral disruption during the test trial.

Based on the results of previous research, several specific predictions were made for the present experiment. A primary expectation was that scopolamine would impair memory processes. Because both glucose and insulin can act as acetylcholine agonists, we hypothesized that each of these agents would attenuate the scopolamine-induced amnesia and that their combination would allow greater attenuation of memory impairment by scopolamine than would either agent alone. However, in the absence of scopolamine, glucose and insulin combinations should lead to memory performance similar to that of glucose alone. We also predicted that glucose and insulin combinations would yield an additive effect only during scopolamine administration because insulin was expected to facilitate memory processes only under conditions of impairment (i.e., impaired glucose utilization, decrease in acetylcholine activity). Whereas insulin was not expected to have any effects on memory retention in the absence of scopolamine, glucose was predicted to enhance memory independent of scopolamine administration.

METHOD

Subjects

Subjects were nine male rats (Long-Evans strain), with a mean weight of 400 g. The rats were about 10 months old at the time of initial training and were housed in single cages with light onset at 0700 and offset at 1900. Experimental procedures were conducted between 1000 and 1600. Subjects had continuous access to water, but food was restricted, as described below.

Apparatus

An eight-arm radial maze was constructed of white plastic with arms ($79.2 \times 10.2 \times 6.8$–$13.5$ cm.) extending from a central circular platform that had a diameter of 23.6 cm. The maze was equipped with eight detachable doors (10.2×20.3 cm), each of which could block the entrance into an arm. The maze was elevated 1 m above the floor and was located in a small room (2.8×2.8 m). The maze was surrounded by stable visual cues (the observer, a door, a chair, two overhead lights, and two

ceiling vents). In addition, each arm was distinguishable by a black geometric shape located at the end of each arm. These cues were different for each arm and remained in the same location throughout the study. At the end of each arm were opaque cups (5.6 cm in diameter) that contained the cereal Fruit Loops (Kellogg's), which acted as food reinforcement. Blood glucose was measured by a Lifescan One Touch II glucometer and First Choice test strips.

Drugs

The following drug doses and concentrations were used: glucose 100 mg/kg, 100 mg/ml; scopolamine hydrochloride 2 mg/kg, 2 mg/ml; and insulin (Lilly Regular Iletin Insulin) 0.4 units/kg, 0.4 units/ml. All drugs were dissolved in or diluted with normal saline solution. For control treatments (drug dose = 0), rats were injected with equivalent volumes of saline solution.

Procedure

Training phase. The food ration was restricted until the rats reached 85% of predeprivation body weight. This weight was maintained throughout the experiment. The rats were fed daily after completing the maze task.

Initially, the rats were adapted to the maze for 3 days. This adaptation consisted of placing the rat in the maze that had been baited with three pieces of food reinforcement per arm and allowing 20 min for eating and maze exploration. After adaptation, training began.

On each training trial, four randomly chosen arms were blocked, and the four unblocked arms were baited with food reinforcement. The rat was then placed on the central circular platform, facing one of the blocked arms, and given 4 min to collect the four reinforcements. The rat was removed and replaced in the home cage after eating all food reinforcements or when 4 min had elapsed, whichever came first. The maze was then wiped clean, and the four detachable doors were removed. The arms that were previously blocked/unentered were now baited, and the previously unblocked/entered arms were left unbaited. After a delay, the rat was again placed into the maze, facing an arm that was not baited. The rat was allowed 8 min to collect all four reinforcements. After collecting the reinforcement or after 8 min, whichever came first, the rat was removed. A full entry (back feet across the threshold) into an arm that was unblocked/entered during the acquisition trial was scored as an error in memory retention. Additional entries into arms that had already been visited during the second trial were each scored as an error in working memory. Working memory scores were not of primary interest in this study but were recorded, as was the time required to run the maze. All data were based on visual observations and were recorded manually by the observer.

In the beginning of training, the delay between the acquisition and test trials was very short but increased as training continued. The delay began at 0 min and remained at that interval until the rat had reached a criterion performance level of completing the task within 8 min, making no more than two errors in memory retention for two consecutive test trials. Delay periods were increased by 5 min, 15 min, and 1-h increments until the final delay period of 5 h was reached. After performance appeared to have stabilized at approximately 1.25 errors in memory retention at a 5-h delay, the training phase was concluded. An average of slightly over one error was chosen as a criterion of memory performance to avoid possible "ceiling" and "floor" effects during the testing phase.

TABLE 1

ORDER OF TREATMENTS FOR SUBJECTS AND MEAN ERRORS FOR EACH DAY POOLED ACROSS TREATMENTS

	Order of Drug Treatments							
	1st	2nd	3rd	4th	5th	6th	7th	8th
Rat A	GI	GS	S	GIS	IS	G	I	W
Rat B	S	GI	G	IS	GIS	GS	W	I
Rat C	GIS	IS	GI	I	GS	W	S	G
Rat D	G	I	GIS	W	S	IS	GI	GS
Rat E	GI	I	GS	S	W	GIS	G	IS
Rat F	W	GIS	IS	S	G	I	GS	GI
Rat G	GS	W	I	G	GI	S	GIS	IS
Rat H	I	G	GS	GI	W	GIS	IS	S
Rat I	GS	GIS	I	G	S	GI	IS	W
	Mean Errors for Each Day Pooled Across Drug Treatments							
	2.0	1.22	1.88	1.44	1.11	1.22	1.44	0.77

*G = glucose, I = insulin, S = scopolamine, W = saline.

After training was completed, one test trial without an acquisition trial was conducted for each subject. This "memory control" was done to ensure that the performance of the subjects depended on learning and retaining which arms were visited during the acquisition trial rather than some other process such as olfactory sense. As expected, all subjects demonstrated poor maze performance, making either 3 or 4 out of a possible 4 errors in "memory retention."

Testing phase. The procedure during the testing phase was the same as that for training with the exceptions of having one predetermined delay interval (5 h) between trials and the administration of drug injections immediately after the acquisition trial. In addition, one subject was removed from the study during experimental trials because, on introduction to drug injections, no entries were made during the test trial, regardless of drug conditon.

Each of the remaining nine subjects experienced the eight drug conditions, each condition being one of the factorial combinations of the two doses of each drug, with one dose being zero (no drug). For all subjects, the sequence of conditions (drug treatment combinations) was predetermined. Eight of the initial 10 subjects were chosen randomly to be included in an 8×8 matrix, which placed each drug treatment in every position of the sequence. For the remaining two subjects, the treatment sequence was determined randomly. Neither of the random sequences matched any other sequence. See Table 1 for the specific order of drug treatments administered to all subjects included in the study.

During the test phase, animals were injected and run in the maze every other day, allowing 48 h between drug treatments to minimize carry-over effects from the previous test. Repeated scopolamine treatments have been used by other researchers in radial arm maze studies (6,22), illustrating that such procedures are conventional for within-subject designs. Drugs were injected intraperitoneally at the dosages previously indicated. When there was no administration of a particular drug (dose = 0), an equivalent amount of saline solution was injected.

After all behavioral testing was finished, blood glucose tests were conducted in order to measure the effects of some of the drug treatments on blood glucose levels. Over a period of 4 days, the subjects were injected with glucose, insulin, glucose +

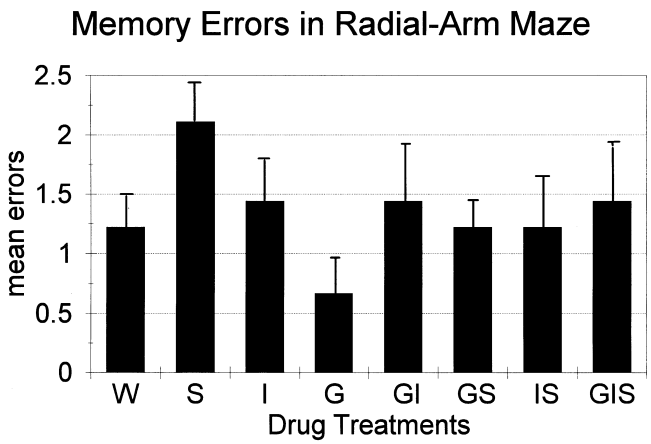

FIG. 1. Mean memory errors ($n = 9$) in the radial arm maze for each drug treatment. W = saline control, S = scopolamine 2 mg/kg, I = insulin 0.4 unit/kg, G = glucose 100 mg/kg, GI = glucose + insulin, GS = glucose + scopolamine, IS = insulin + scopolamine, GIS = glucose + insulin + scopolamine. See text for description of significance of differences.

insulin, and saline solution at the doses used during the memory experimentation trials. The blood samples were taken by pricking the rat's tails with a lancet and were then analyzed with the glucometer. The samples were taken 20–30 min after insulin and glucose + insulin injections, 15–25 min after saline injections, and 10–20 min after glucose injections. For these tests, food deprivation (24 h) conditions were very similiar to those during the behavioral tests.

RESULTS

The subjects required a mean of 31.2 training sessions to demonstrate moderate competency and stability in task performance (i.e., a mean memory error no greater than 1.2 incorrect entries for at least two consecutive sessions). The range was 24–39 training sessions.

Table 1 lists the mean errors for each day pooled across drug treatments. Group means do not indicate that performance changed appreciably as a function of the order of testing.

The group mean memory errors for each of the eight drug conditions are indicated in Fig. 1.

To test for significant differences between the drug conditions, *t*-tests for planned comparisons among several means were performed according to procedures described in Bruning and Kintz (5). This test was choosen because several specific a priori hypotheses regarding the differences between particular groups had been made. A critical difference of 0.82 (two-tailed) between the means was required to obtain a significant difference level of $p < 0.05$. This analysis indicated a significant difference between the saline treatment (W; mean ± SEM = 1.22 ± 0.47) and the scopolamine treatment (S; 2.11 ± 0.76). Scopolamine significantly increased the number of memory errors relative to that of saline controls.

A significant difference between the glucose + scopolamine treatment (GS; 1.22 ± 0.49) and the scopolamine treatment was found. Glucose + scopolamine resulted in a lower number of memory errors than scopolamine.

A significant difference between the insulin + scopolamine condition (IS; 1.22 ± 0.44) and the scopolamine condition was found. Insulin + scopolamine resulted in a lower number of memory errors than scopolamine.

No other group differences were significant, although the differences glucose + insulin + scopolamine (GIS; 1.44 ± 0.64) vs. scopolamine, glucose (G; 0.67 ± 0.34) vs. saline and glucose + insulin (GI; 1.44 ± 0.60) vs. glucose approached significance. The mean for the insulin condition (I) was 1.44 errors (±0.58).

To determine the interactive effects of insulin, glucose and scopolamine on the percentage of memory errors, a three-way within-subjects analysis of variance was performed. Results indicated no significant main effects for insulin, glucose or scopolamine. No significant three-way interaction between insulin, glucose and scopolamine was found, but a significant two-way interaction between insulin and glucose was found [$F(1,56) = 4.14$, $p < 0.05$]. This interaction indicates an antagonistic pattern; each treatment tended to weaken the effect of the other.

No significant two-way interaction between glucose and scopolamine was found. The lack of an interaction between these treatments indicates that glucose tended to decrease memory errors in both scopolamine and no-scopolamine conditions.

A significant two-way interaction between insulin and scopolamine was found [$F(1,56) = 4.14$, $p < 0.05$]. This interaction indicates that insulin attenuated scopolamine's effect of increasing memory errors but had no effect on memory in the no-scopolamine condition.

Simple analysis of variance for repeated measures demonstrated that working memory errors were not affected by drug treatment [$F(7,56) = 0.44$, $p < 0.87$]. The *t*-tests for planned comparisons among several means were not used because no a priori hypotheses regarding particular group differences in working memory errors were made.

Postexperimental blood glucose tests indicated that the drug treatments had no measurable effect on blood glucose levels approximately 15 min after glucose injections and 25 min after insulin injections. Correspondingly, combinations of insulin and glucose had no detectable effect on blood glucose 25 min after its administration. Mean blood glucose levels (mg/dl) were 80.9 (±3.1) for saline controls, 79.9 (±2.5) for glucose, 78.1 (±2.9) for insulin and 77.9 (±3.2) for glucose + insulin.

DISCUSSION

The findings of the present study are consistent with some previous findings regarding pharmacological modulation of memory. Scopolamine interrupted memory performance, as reported by Beatty et al. (3) and numerous other investigators. Both insulin and glucose attenuated the detrimental effect of scopolamine on memory performance, as reported by Messier and Destrade (24) and Messier et al. (25). Insulin by itself had no effect on memory performance (27). The present experiment has extended the generality of these previously reported effects of glucose and insulin on scopolamine-produced amnesia by demonstrating the interaction in the radial arm maze, a paradigm widely used in the investigation of learning and memory.

A definite trend for a beneficial effect of glucose on memory in normal (no-scopolamine) conditions was seen, although it was not significant, unlike in previous studies, which found a significant memory-enhancing effect of glucose (15,27,28).

Working memory was not affected by any of the drug treatments. Therefore, memory retrieval processes appear to have been unaffected during the test trial.

The hypothesis that a combination of insulin and glucose would attenuate the effects of scopolamine to a greater extent than either insulin or glucose alone was not supported. In fact,

because a significant two-way antagonist interaction was found between insulin and glucose, the present results suggest instead that combining insulin and glucose results in an attenuation of the effect of scopolamine to a smaller degree than that of either agent alone.

Significant differences were not seen in blood glucose (BG) levels between glucose, insulin, glucose + insulin and saline controls. Insulin did reverse the effects of scopolamine, so the insulin reversal of the effect of scopolamine on memory retention seen in the Messier and Destrade study (24) may not have been due to a hypoglycemic counterregulatory release of epinephrine. However, this hypothesis cannot be ruled out.

That differences in BG levels were not detected is a rather surprising result, particularly with regard to the absence of hyperglycemia in response to glucose administration. Two things should be noted here. First, BG testing was done postexperimentally, and thus the BG levels obtained may not reflect the actual BG levels during memory testing. Second, blood glucose testing was done only once after drug injections. Changes in blood glucose levels of these food-deprived rats may have occurred outside of the time interval in which testing was conducted. It is quite likely, for example, that glucose levels increased immediately after glucose injection and returned to baseline prior to testing (approximately 15 min postinjection).

Assuming that the BG test results in the present study accurately reflect BG levels throughout the intertrial delay during experimentation, the antagonistic interaction between glucose and insulin is particularly difficult to explain. This assumption that BG levels were unaffected by the different drug conditions prevents the two-way interaction from being interpreted as a function of increasing and decreasing glucose availability. Because no drug treatment effects on BG levels were detectable, the glucose–insulin interaction could be a function of some mechanism not directly associated with BG levels.

In support of this proposal, the effect of glucose on memory does not always appear to be directly related to BG levels. Messier and White (27) observed that although 1, 2 and 3 g/kg of glucose resulted in equivalent increases in BG levels, only 2 g/kg facilitated memory performance. They also demonstrated an insulin–glucose interaction in which higher doses of glucose continued to facilitate memory beyond the optimal 2 g/kg dose. They concluded that, because BG levels were not a critical factor in memory performance, this insulin–glucose shift to higher doses was not the result of a need for higher doses of glucose to compensate for a reduction of BG levels in the presence of insulin. In other words, the insulin–glucose interaction found in their study could not be explained adequately as a function of BG levels.

Other researchers have noted that factors unrelated to blood glucose levels per se may account for the relation of glucose to memory function. Glucose may directly affect CNS acetylcholine activity (25,35,40), and the effects of glucose may be mediated in the CNS by insulin (4,24). Furthermore, insulin itself has been implicated in acetylcholine activity (21,24). Thus, both glucose and insulin may affect memory processes independent of their effects on BG levels, perhaps by facilitating acetylcholine activity. This observation is consistent with the results of the present study and those of other studies.

Ragozzino et al. (31) demonstrated that in rat subjects hippocampal acetylcholine release is increased during spontaneous alternation testing and is further augmented by glucose administration.

With regard to the influence of insulin on acetylcholine activity, insulin induces acetylcholine receptor cluster formation in muscle cells (1). In addition, an insulin analogue (insulin-like growth factor II) enhanced choline acetyltransferase activity in mouse septal cholinergic neuron cultures (19). Hoyer (17) discussed deficits in acetylcholine following desensitization of the neuronal insulin receptor in Alzheimer disease. He proposed that reduced insulin receptor response decreases the initiation of glycolysis, during which acetylcholine is normally produced.

Memory improvement following glucose administration follows a dose–response curve that can be described as an inverted U (15). An interesting question that has not been answered is whether this inverted-U function would generalize to the ability of glucose to reverse the detrimental effects of scopolamine on memory. If such a function does exist and the reversal of insulin on the effect of scopolamine also follows a nonlinear dose–response curve, then the failure of the present study to find an additive effect from combined glucose and insulin administrations could be explained as a result of using glucose and insulin doses that were too high to demonstrate an additive effect. Because only one dose of these substances was used and because this dose was comparable to that of previous studies that demonstrated a maximal effect, combining them may have produced a response beyond the peak of a biphasic dose–response curve. Only future studies using a wide range of doses of glucose and insulin combined with scopolamine administration will determine whether this explanation is valid.

That insulin can affect memory in a complex, nonlinear, dose-dependent fashion is consistent with the seemingly incompatible findings of some previous investigations. Some studies have found that insulin may enhance memory and act as an acetylcholine agonist, whereas other studies have found that insulin can impair memory and act as an acetylcholine antagonist.

For example, the present study and the study by Messier and Destrade (24) have shown that insulin can facilitate memory retention by attenuating the effect of acetylcholine antagonist scopolamine. In addition, protection of working memory against ischemia was seen among rats treated with insulin (39). Rats treated with IVT insulin injections demonstrated better performance on a passive-avoidance task (29).

However, Santucci et al. (33) found that insulin caused impairments in a 24-h retention of passive avoidance. Another study (20) demonstrated that insulin can impair memory retention on an avoidance task. The impairment was described as following a U-shaped dose–response curve. Furthermore, insulin facilitates the memory-impairing effects of anticholinergic drugs.

Perhaps insulin administration can enhance or impair memory, depending on resulting physiological levels of insulin. Too much insulin may decrease BG levels to such an extent as to make glucose unavailable for cells implicated in memory (i.e., acetylcholine-synthesizing cells). Slight elevations in insulin may allow more glucose to be utilized by cells involved in memory processes.

In addition, insulin may directly affect the central cholinergic system. At least two other memory studies (20,24) have shown that insulin can interact with cholinergic drugs. However, the direction of this interaction has varied. Whether insulin facilitates or attenuates the effect of these drugs may very well depend on dose. At present, the nature of the apparent interaction between insulin and acetylcholine is poorly understood and is an interesting question for further investigation.

ACKNOWLEDGEMENTS

The First Choice test strips used for blood glucose measurement were generously donated by Polymer Technology International.

REFERENCES

1. Baker, L. P.; Peng, H. B.: Induction of acetylcholine receptor formation by local application of growth factors in cultured Xenopus muscle cells. Neurosci. Lett. 185:135–138; 1995.
2. Baskin, D. G.; Figlewicz, D. P.; Woods, S. C.; Porte, D.; Dorsa, D. M.: Insulin in the brain. Ann. Rev. Physiol. 49:335–347; 1987.
3. Beatty, W. W.; Butters, N.; Janowsky, D. S.: Patterns of memory failure after scopolamine treatment: implications for cholinergic hypotheses of dementia. Behav. Neural Biol. 45:196–211; 1986.
4. Boyd, F. T.; Clarde, D. W.; Muther, T. F.; Raizada, M. K.: Insulin receptors and insulin modulation of norepinephrine uptake in neuronal cultures from rat brain. J. Biol. Chem. 260:15880–15884; 1985.
5. Bruning, J. L.; Kintz, B. L.: Computational handbook of statistics. Glenview, Illinois: Scott, Foresman and Company; 1977.
6. Buresova, O.; Bures, J.: Radial maze as a tool for assessing the effect of drugs on the working memory for rats. Psychopharmacology 77:268–271; 1982.
7. Cooper, J. R.; Bloom, F. E.; Roth, R. H.: Acetylcholine. In: House, J., ed. The biochemical basis of neuropharmacology. New York: Oxford University Press; 1986:173–202.
8. Costa-Miserachs, D.; Portell-Cortes, I.; Marti-Nicolovius, M.; Morgado-Bernal, I.: La adrenalina: un sistema endogeno de odulacion de la memoria. Psicothema 7:113–128; 1995.
9. Costa-Miserachs, D.; Portell-Cortes, I.; Aldavert-Vera, L.; Torras-Garcia, M.: Long-term memory facilitation in rats by posttraining epinephrine. Behav. Neurosci. 108:469–474; 1994.
10. Costa-Miserachs, D.; Portell-Cortes, I.; Aldavert-Vera, L.; Torras-Garcia, M.: Facilitation of a shuttlebox conditioning with posttraining epinephrine in rats. Behav. Neural Biol. 60:75–78; 1993.
11. Craft, S.; Dagogo-Jack, S. E.; Wiethop, B. V.; Murphy, C.; Nevins, R. T.; Fleischman, S.; Rice V.; Newcomer, J. W.; Cryer, P. E.: Effects of hypoglycemia on memory and hormone levels in dementia of the Alzheimer type: a longitudinal study. Behav. Neurosci. 107:926–940; 1993.
12. Craft, S.; Zallen, G.; Baker, L. D.: Glucose and memory in mild senile dementia of the Alzheimer type. J. Clin. Exp. Neuropsychol. 4:253–267; 1992.
13. Darolia, M. K.; Yadava, A.; Malhotra, S.: Effect of epinephrine on learning under anesthesia. J. Indian Acad. Appl. Psychol. 19: 47–51; 1993.
14. Durkin, T.: Central cholinergic pathways and learning and memory processes: presynaptic aspects. Comp. Biochem. Physiol. 93A: 273–280; 1989.
15. Gold, P. E.; Vogt, J.; Hall, J. L.: Posttraining glucose effects on memory: behavioral and pharmacological characteristics. Behav. Neural Biol. 46:145–155; 1986.
16. Hall, J. L.; Gonder-Frederick, L. A.; Chewning, W. W.; Silveira, J.; Gold, P. E.: Glucose enhancement of performance on memory tests in young and aged humans. Neuropsychologia 27:1129–1138; 1989.
17. Hoyer, S.: Neurodegeneration, Alzheimer's disease, and beta-amyloid toxicity. Life Sci. 55:1977–1983; 1994.
18. Introini-Collison, I.; Saghafi, D.; Novack, G. D.; McGaugh, J. L.: Memory-enhancing effects of post-training dipivefrin and epinephrine: involvement of peripheral and central adrenergic receptors. Brain Res. 572:81–86; 1992.
19. Konisha, Y; Takahashi, K; Chui, D. H.; Rosenfeld, R. G.; Himeno, M.; Tabira, T.: Insulin-like growth factor II promotes in vitro cholinergic development of mouse septal neurons: comparison with the effects of insulin-like growth factor I. Brain Res. 649:53–61; 1994.
20. Kopf, S. R.; Baratti, C. M.: The impairment of retention induced by insulin in mice may be mediated by a reduction in central cholinergic activity. Neurobiol. Learning Mem. 63:220–228; 1995.
21. Kyriakis, J. M.; Hausman, R. E.; Peterson, S. W.: Insulin stimulates choline acetyltransferase activity in cultured embryonic chicken retina neurons. Proc. Natl. Acad. Sci. USA 84:7463–7467; 1987.
22. Magnani, M.; Pozzi, O.; Biagetti, R.; Banfi, S.; Dorigotti, L.: Oxiracetam antagonizes the disruptive effects of scopolamine on emory in the radial maze. Psychopharmacology 106:175–178; 1992.
23. Marfaing, P.; Penicaud, L.; Groer, Y.; Mraovitch, S., Calando, Y.; Picon, L.: Effects of hyperinsulinemia on local cerebral insulin binding and glucose utilization in normoglycemic awake rats. Neurosci. Lett. 115:279–285; 1990.
24. Messier, C.; Destrade, C.: Insulin attenuates scopolamine-induced memory deficits. Psychobiology 22:16–21; 1994.
25. Messier, C.; Durkin, T.; Mrabet, O.; Destrade, C.: Memory-improving action of glucose: indirect evidence for a facilitation of hippocampal acetylcholine synthesis. Behav. Brain Res. 39:135–143; 1990.
26. Messier, C.; Gagnon, M.: Glucose regulation and cognitive functions: relation to Alzheimer's disease and diabetes. Behav. Brain Res. 75:1–11; 1996.
27. Messier, C; White, N. M.: Memory improvement by glucose, fructose, and two glucose analogs: a possible effect on peripheral glucose transport. Behav. Neural Biol. 48:104–127; 1987.
28. Packard, M. G.; White, N. M.: Effect of posttraining injections of glucose on acquisition of two appetitive learning tasks. Psychobiology 18:282–286; 1990.
29. Park, C. R.; Seeley, R. J.; Woods, S. C.: ICV insulin increases performance on a passive-avoidance task. Soc. Neurosci. Abstr. 21: 377.14; 1995.
30. Piercy, M. F.; Vogelsang, G. D.; Franklin, S. R.; Tang, S. H.: Reversal of scopolamine-induced amnesia and alterations in energy metabolism by the nootropic piracetam: implications regarding identification of brain structures involved in consolidation of memory traces. Brain Res. 424:1–9; 1987.
31. Ragozzino, M. E.; Unick, K. E.; Gold, P. E.: Hippocampal acetylcholine release during spontaneous alternation testing: augmentation by glucose. Soc. Neurosci. Abstr. 21:69.11; 1995.
32. Richardson, J. T. E.: Cognitive function in diabetes mellitus. Neurosci. Biobehav. Rev. 14:385–388; 1990.
33. Santucci, A. C.; Schroeder, H.; Riccio, D. C.: Homeostatic disruption and memory: effect of insulin administration in rats. Behav. Neural Biol. 53:321–333; 1990.
34. Stone, W. S.; Rudd, R. J.; Gold, P. E.: Amphetamine, epinephrine, and glucose enhancement of memory retrieval. Psychobiology 18:227–230; 1990.
35. Stone, W. S.; Rudd, R. J.; Gold, P. E.: Glucose attenuation of paradoxical sleep deficits in old rats. Behav. Neural Biol. 5:79–86; 1992.
36. Stone, W. S.; Rudd, R. J.; Gold, P. E.: Glucose attenuation of scopolamine- and age-induced deficits in spontaneous alternation behavior and regional brain (-sup-3H)2-deoxyglucose uptake in mice. Psychobiology 20:270–279; 1992.
37. Stone, W. S.; Rudd, R. J.; Ragozzino, M. E.; Gold, P. E.: Glucose attenuation of deficits in memory retrieval in altered light:dark cycles. Psychobiology 20:47–50; 1992.
38. Stone, W. S.; Walser, B.; Gold, S. D.; Gold, P. E.: Scopolamine- and morphine-induced impairments of spontaneous alternation performance in mice: reversal with glucose and with cholinergic and adrenergic agonists. Behav. Neurosci. 105:264–271; 1991.
39. Strong, A. J.; Fairfield, J. E.; Monteiro, E.; Kirby, M., Hogg, A. R., Snape, M., Ross-Field, L.: Insulin protects cognitive function in experimental stroke. J. Neurol. Neurosurg. Psychiatr. 53: 847–853; 1990.
40. Tucek, S.: Acetylcoenzyme A and the synthesis of acetylcholine in neurons: review of recent progress. Gen. Physiol. Biophys. 2:313–324; 1983.