Diabetes mellitus (DM) has become a major and growing health concern. The number of Americans suffering with DM has tripled in the last twenty years, and the number of individuals developing DM especially Type II (insulin resistant form) has increased at an alarming rate. A major concern is the increased risk of developing Alzheimer’s disease (AD) with DM. The goal here was to examine the effects of the induction of DM on memory.

Make Long-Evans rats were trained in a delayed-match-to-place (DMP) task of the Morris water maze. The advantage of using this task was that the animals had to learn and remember something new each time they were tested. After good initial performance was achieved, some rats were treated with streptozotocin to destroy insulin-producing cells in the pancreas and induce Type I DM. Other rats were placed on a high-fat diet, with or without streptozotocin treatment, to induce insulin resistance and Type II DM. Appropriate control groups were included for both conditions. Body weights and blood glucose levels were monitored in all animals.

The rats were evaluated in the DMP task at monthly intervals. Type I rats did not develop memory impairments, even 12 weeks after treatment. These animals could not be tested at longer intervals due to morbidity. Type I rats that showed significant cognitive impairments were only rats that had received the high-fat diet and streptozotocin treatment. This pattern of results suggests that both the loss of insulin receptor function and insulin itself are important for developing memory impairments with DM. Alternatively, oxidative stress induced by the high-fat diet could potentially contribute to damage in the memory centers of the brain, and insulin loss to produce memory deficits.

**Goals**

- To develop and evaluate a delayed-match-to-place (DMP) paradigm that allows for repeated memory testing
- To determine whether models of Type I and Type II diabetes develop memory deficits

**Methods**

**Subjects.** Long Evans Rats were obtained from Harlan Laboratories at 8 weeks of age. All animals were fed standard rodent chow with ad libitum access to water during the initial training phase on the DMP task.

**Behavioral Testing.** Spatial memory was evaluated using a delayed-match-to-place paradigm in a water maze (1). Briefly, the goal of the task was to locate a hidden platform on a pool (8 ft diameter) of water. The location of the platform changed every day. Each day the rats were given a training trial (90 seconds maximum duration). After a delay period of either 1 or 90 minutes the rats were given another trial (Trial 2) to test their memory. Following two more trials at an interval of 30 seconds to reinforce their performance. If a rat did not find the platform on the training trial, its data was not included in the analysis. It was found that the results using the 1 or 90 minute delay intervals were not different, so the data were combined for the analyses presented here.

**Type I DM Model.** At approximately 16 weeks the rats were fasted for 8 hours, anesthetized using urethane, and given an i.p. injection of either streptozotocin (80 mg/kg) at a concentration of 22.5 mg/ml in a p.r. 4.5 sodium citrate buffer solution or just buffer solution (2). Blood glucose levels in STZ treated rats were obtained 72 hours later. STZ treated rats under the 200 mg/dl criterion received another injection of STZ at the same dose. Body weights were recorded weekly and blood glucose levels were obtained every 4 weeks. The rats were retested in the DMP task at 4, 8, and 12 weeks post-injection.

**Type II DM Model.** At approximately 16 weeks rats were divided into 4 experimental groups. 1) Low Fat diet 2) Low fat diet + STZ treatment 3) High fat diet 4) High fat diet + STZ. Animals were given ad libitum access to research diets (from Research Diets, Inc., New Brunswick NJ). Low fat diet − 10% total kcal from fat. Low fat diet + 15% total kcal from fat for the remainder of the experiment. 4 weeks after placement on experimental diets, the rats were fasted for 8 hours, anesthetized using urethane, and given an i.p. injection of either streptozotocin (25 mg/kg) at a concentration of 22.5 mg/ml in a p.r. 4.5 sodium citrate buffer solution or just buffer solution (2). Blood glucose levels in STZ treated rats were obtained 72 hours later. Body weights were recorded weekly and blood glucose levels were obtained every 4 weeks. The rats were retested in the DMP task at 4 and 8 weeks post injection. Research is being continued on this group.

**Conclusions**

**Type 1 Model**

- STZ treated rats lost weight, while the weights of the control group increased over time.
- STZ treated rats had significantly higher blood glucose levels than the control group.
- STZ did not affect the rats’ ability to remember in the DMP task for up to 12 weeks after treatment.

**Type 2 Model**

- No differences in body weight were seen by 8 weeks after treatment. Weight gain might have been expected in the rats fed the high fat diet.
- STZ treated groups had increased blood glucose levels compared to the vehicle injected control groups. Combined treatment with the high fat diet plus STZ showed the earliest and greatest increases in blood glucose levels.
- Only the HF & STZ group developed memory impairment.

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**References**