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The effect of parents' diabetes on memory and learning in Rats' Offspring'

Alireza Sarkaki[*1], Shiva Ahmadian[2], Mohammad Badavi [1], Yaghoub Farbood[1]

1. Department of Physiology, Persian Gulf Physiology Research Center, Faculty of Medicine, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran.
2. Department of Biology, Sciences Faculty, Islamic Azad University, Kazeroon Branch, Kazeroon ,Iran.

*Corresponding Author: Alireza Sarkaki. Department of Physiology, Persian Gulf Physiology Research Center, Faculty of Medicine, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran.

Cell phone: +986133738264
Email: sarkaki145@gmail.com

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Introduction: Parental diabetes may influence risk factors in the offspring and are difficult to identify without accurate dates of diagnosis. The Aim of this study was to evaluate the effect of paternal and maternal diabetes type 1 on spatial learning and memory of adult male and female rats' offspring.

Materials and Methods: Wistar adult male and female rats were divided randomly in control (healthy) and diabetic groups. In order to mate 5 females+3 males were placed in each cage and grouped as following: 1) NMNF (normal males coupled with normal femals), 2) NMDF (normal males coupled with diabetic females), 3) DMNF (Diabetic males coupled with normal females), and 4) DMDF (both males and females were diabetic and coupled). In order to make the animal model of diabetes healthy male and female rats received a single dose of sterptozotocin (STZ, 60 mg/kg, i.p.) and their blood glucose higher than 250 mg/dl recorded as diabetic state 5 days after STZ injection. Adult offspring (both sexes separately, at least 85-90 days old) were tested in Morris water maze (MWM) for spatial learning and memory 4 trials daily for 4 consecutive days and followed by a single trial as probe (memory test) 24 h later.

Results: Spatial learning of male offspring with paternal or maternal diabetes alone was impaired while it did not in female offspring (with except for swimming speed). In other hand memory of both sexes' offspring with one or both diabetic parents was improved significantly.

Conclusions: It may be concluded; that offspring obtained from diabetic parents (one or both of them) have a risk for cognitional behavior in adult life at least at an early age. However, little is known about the precise biological process behind these effects in later life.

Keywords: Parental diabetes; offspring; spatial cognition; Morris water maze; rat

Introduction

Cause of death in western society, with associated risks of hypertension, coronary heart disease, stroke, diabetes, and breast, prostate and colon cancer (Wichi et al., 2005, Penesova et al., 2011). Recent epidemiologic data indicate an increased risk of Alzheimer's disease in association with adult diabetes induced obesity. There is no convincing evidence that, in both human and animal models, the in utero environment may impact on fetal developmental processes, altering offspring homeostatic regulatory mechanisms.

"Gestational programming" may result in altered cell number, organ structure, hormonal set points or gene expression, with effects being permanent or expressed only at select offspring ages (e.g., newborn, adult) (Ross et al., 2007). Paternal and maternal type 2 diabetes, exclusive of gestational diabetes, may influence risk factors in the offspring differently (through possible epigenetic effects of parental diabetes) and are difficult to identify without accurate dates of diagnosis (Penesova et al., 2010).

Epidemiological and experimental studies have led to the hypothesis of the fetal origin of adult diseases, suggesting that some adult diseases might be determined before birth by altered fetal development. Little is known about the long-term consequences of in utero exposure to maternal diabetes (Nehiri et al., 2008). Population-based studies have shown that the offspring of diabetic mothers have an increased risk of developing obesity, insulin resistance, type 2 diabetes and hypertension in later life (Fujisawa et al., 2007).

Maternal diabetes affects the development of the offspring by altering the uterine environment. Maternal diabetes causes decreased expression of anti-oxidative enzymes and enhanced angiogenesis in the offspring in rats (Zabihi et al., 2008). It has suggested that children of diabetic mothers are at increased risk for a variety of developmental disturbances (Rizzo et al., 1997).

The offspring of diabetic mothers (ODM) have an increased risk of developing metabolic and cardiovascular dysfunction. However, few studies have focused on susceptibility to disease in offspring of mothers developing diabetes during pregnancy (Segar et al., 2009).

The behavioural alterations observed in the offspring were comparable to the behavioural alterations noted in Streptozotocine (STZ) diabetic rat. Exposure of offspring to the diabetic environment in their foetal life can lead to

anxiogenic/emotional behaviours in adult life. It has shown that offspring of normal female-diabetic male (NFDM) and diabetic female-diabetic male (DFDM) exhibited mild hyperglycaemia. No significant behavioural alterations in the offspring of DFNM were observed (Ramanathan et al., 2000).

Noninsulin-dependent diabetes is being seen more commonly in the pediatric population. Diabetes and impaired glucose tolerance are noted particularly in obese children with a family history of diabetes. In this situation, a glucose tolerance test may be indicated, even in the presence of fasting normoglycemia (Slyper, 1998).

Studies suggest that diabetes during intrauterine development and salt overload beginning at an early age can cause hypertension and renal injury (Rocco et al., 2008). Differentially expressed genes, MAP Kinase, and apoptotic signal pathways play very important roles in hyperglycemia induced neural tube defects (Ma et al., 2009).

It seems that in utero programming during diabetic pregnancy creates a "metabolic memory" which is responsible for the development of obesity in macrosomic offspring. Diabetic pregnancy frequently results in macrosomia or fetal obesity. It seems that the anomalies in carbohydrate and lipid metabolism in macrosomic infants of diabetic mothers are due to maternal hyperglycemia, which leads to fetal hyperinsulinemia (Khan, 2007).

At 60 days of age, rats' pups were tested in an elevated plus-maze to assess differences in emotionality and anxiety. There were no significant differences between offspring of diabetic dams and controls on this measure. All animals were then trained in a radial-arm maze. Results failed to find differences between experimental and control animals. So, it is concluded that the diabetic intrauterine environment has gender-specific effects on central nervous system development (Kinney et al., 2003).

Studies showed that pregnant diabetic rat's delivery was most difficult in diabetic rats fed the high-fat diet. Pups of diabetic rats fed the control diet had growth retardation and increased blood glucose levels. It was concluded that when the mother rat had diabetes, the next generation was also affected (Nasu et al., 2007).

The aim of present study was to assess effects of parental diabetic that at least one or both of them had diabetes family history before mating as well as in utero exposure to maternal diabetes on spatial memory in morris water maze (MWM) as a cognitive function in their adulthood male and female offspring.

Materials and Methods

Animals

Seventy two healthy Wistar rats (3–4 months; weighing 200-250 g, 45 females and 27 males) used in this study were obtained from Ahvaz Jundishapur University of Medical Sciences (AJUMS) central animal house. Animals were housed individually in standard cages under controlled room; temperature (20±2 ◦C), humidity (55-60%) and light exposure conditions 12:12 h light–dark cycle (lighted on 07:00 am) from Jan.30-Oct.30, 2010.

Male and female rats were divided randomly in control (healthy) and diabetic groups. In order to mate 5 females + 3 males were placed in each cage and grouped as following: 1) NMNF (normal males coupled with normal femals), 2) NMDF (normal males coupled with diabetic females), 3) DMNF (Diabetic males coupled with normal females), and 4) DMDF (both males and females were diabetic and coupled).

Access to food and water were ad libitum except during the experiments. Animal handling and experimental procedures performed under observance of the University and Institutional legislation, controlled by the Local Ethics Committee for the Purpose of Control and Supervision of Experiments on Laboratory Animals. All efforts were made to minimize animal suffering, to reduce the number of animals used. Prior to the onset of behavioral testing, all rats were gentle handled for 3 days (daily 5 min).

Their adult offspring (about 85-90 days olds) divided randomly into eight groups on base of their sex differentiation and parental condition. Offspring were obtained from grouped rats by mating a normal male with a normal female (NMNF), normal male with a diabetic female (NMDF), diabetic male with normal female (DMNF) and diabetic male with a diabetic female (DMDF).

Rats were rendered diabetic by injecting streptozotocin (STZ, 60 mg/kg i.p.) in citrate buffer. Only animals with serum glucose levels greater than 250 mg/dl were used. Offspring were subjected to spatial learning and memory tests in Morris water maze (MWM) at the age of 12 weeks. All experiments carried out during the light phase of the cycle (8:00am to 6:00 pm).

Training apparatus

A circular pool was used as described by Morris with some modification (Widy-Tyszkiewicz et al., 2002, Sarkaki et al., 2009). It was a black circular pool (120cm in diameter and 80cm in height) filled with tap water (27±2 ◦C) with a depth 60 cm. The maze divided geographically into four equal size quadrants and release points designed in each quadrant as north (N), east (E), south (S) and west (W).

A hidden circular escape platform (12 cm in diameter) was emerged 2 cm below the water level and was located in the center of the northeast quadrant. Some fixed visual cues including computer, desk, shelves, posters and illumination lights placed on the walls around the pool. A camera positioned above the center of the pool that connected to a computer to record the animal motions. An automated tracking system (Radiab ver. 2, Tehran, Iran) used to measure the escape latency, swimming distance and speed.

Training procedure

Training, took place during the light phase of the cycle between 8:00am and 5:00 pm. Animals were subjected to the training procedure of one session of four trials (block) daily for four consecutive days in the water maze. In each trial, the animals were allowed 60 s to find the platform, then they were allowed to remain there for 30 s, if they did not find the platform within 60 s, animals were gently guided to the platform.

After the completion of a trial, animals were returned to a holding cage for an inter-trial interval of 60 s. After 24 h of the last trial, the platform was removed and the rats were released from the southwest as a probe trial (consisted of a 60 s free swim period) and the time spent in the target quadrant was recorded (Alaei et al., 2008).

Statistical analysis

The results expressed as mean±SEM. Data analyzed by SPSS version 15.0. The statistical tests include two-factor repeated

measures ANOVA, to compare groups in each session, one-way ANOVA to compare groups for total sessions. Post hoc LSD test was performed for inter-groups comparisons. The level of significant was taken as the p-value less than 0.05.

Results

Blood sugar

Fasting blood sugar (FBS) five days after injection of STZ was increased significantly (P<0.01) in diabetic parents rats when compare to before injected of STZ (table 1).

Spatial cognition

Path length

The swimming path length in DMNF offspring (male, female and total of them) was shorter than offspring with maternal diabetes (NMDF group) (#P<0.05, fig. 1a), while it reduced significantly in DMNF female and total offspring significantly related to NMNF (*P<0.05) and DMNF and DMDF offspring (#P<0.05) during 4 days spatial training in water maze (fig. 1b and 1c).

There was no significance difference between swimming path length of NMNF, NMDF and DMDF female offspring.

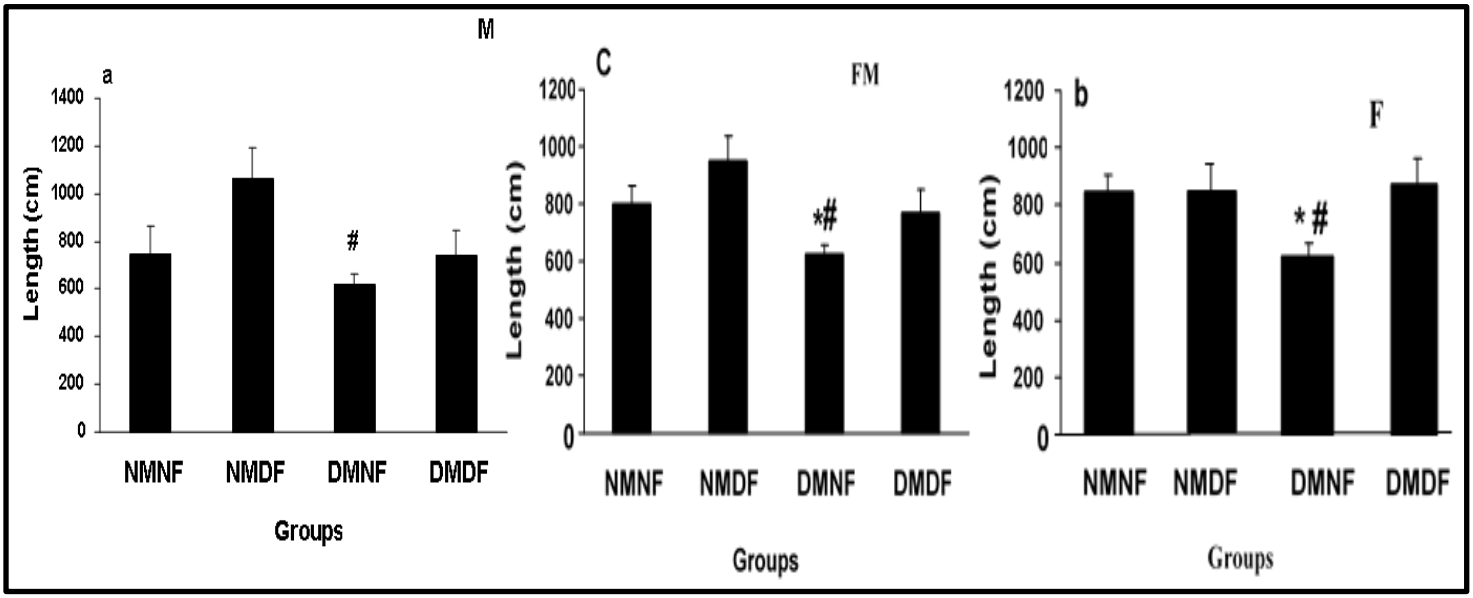

Figure 1: Swimming path length of male (a), female (b) and total male and female (c) offspring during 4 days spatial training in water maze (*P<.05 for NMDF vs. NMNF and #P<.05 for NMDF vs. others groups with one or both diabetic parents respectively).

Latency

The latency to receive the hidden platform during 4 days spatial training in water maze in male and total male and female offspring with paternal diabetes (NMDF and DMDF groups) was shorter than NMDF (#P<0.05, fig. 2a), while it did not difference in female offspring of all groups. (fig. 2b and 2c).

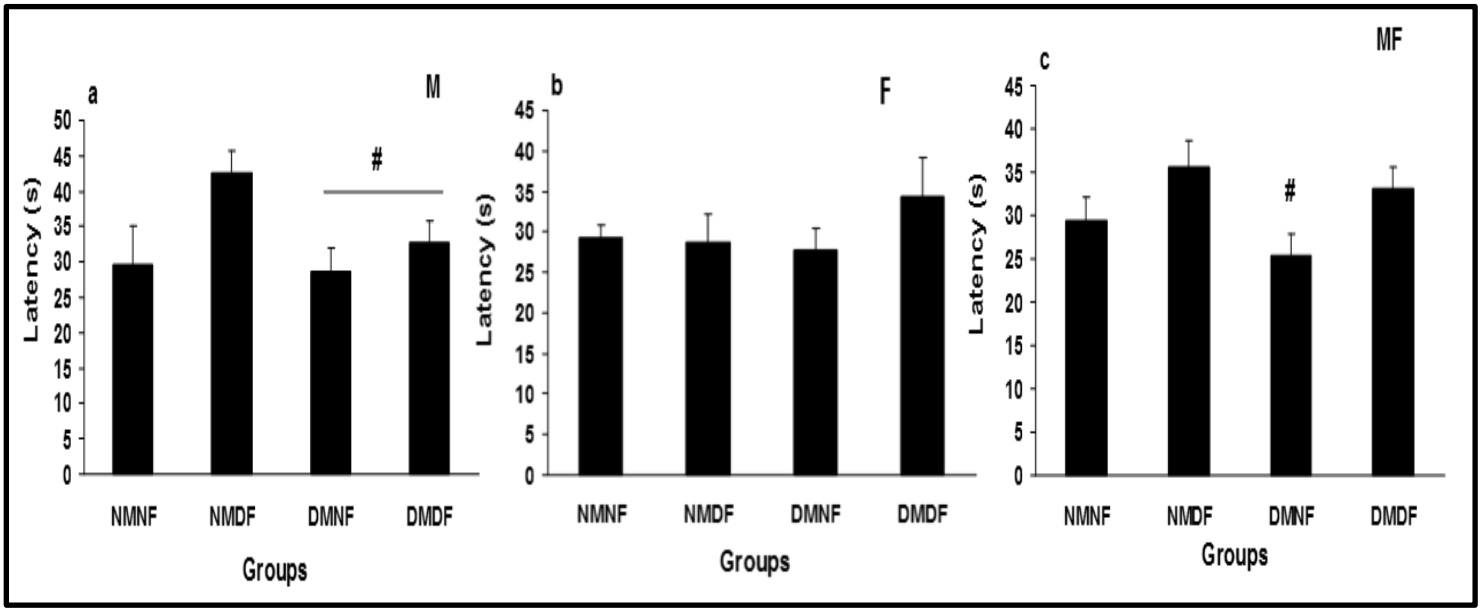

Figure 2: The latency to receive the hidden platform during 4 days spatial training in the water maze in male (a), female (b) and total of male and female (c) offspring (# P<.05 for DMNF and DMDF vs. NMDF groups). There was no difference between groups NMNF with others.

Swimming speed

The speed was not different between male and total offspring in all groups (fig.3a and 3c), while it decreased significantly in female offspring of DMNF and DMDF groups when compare with NMNF (*P<0.05) and NMDF (#P<0.05) groups (fig. 3b and 3c).

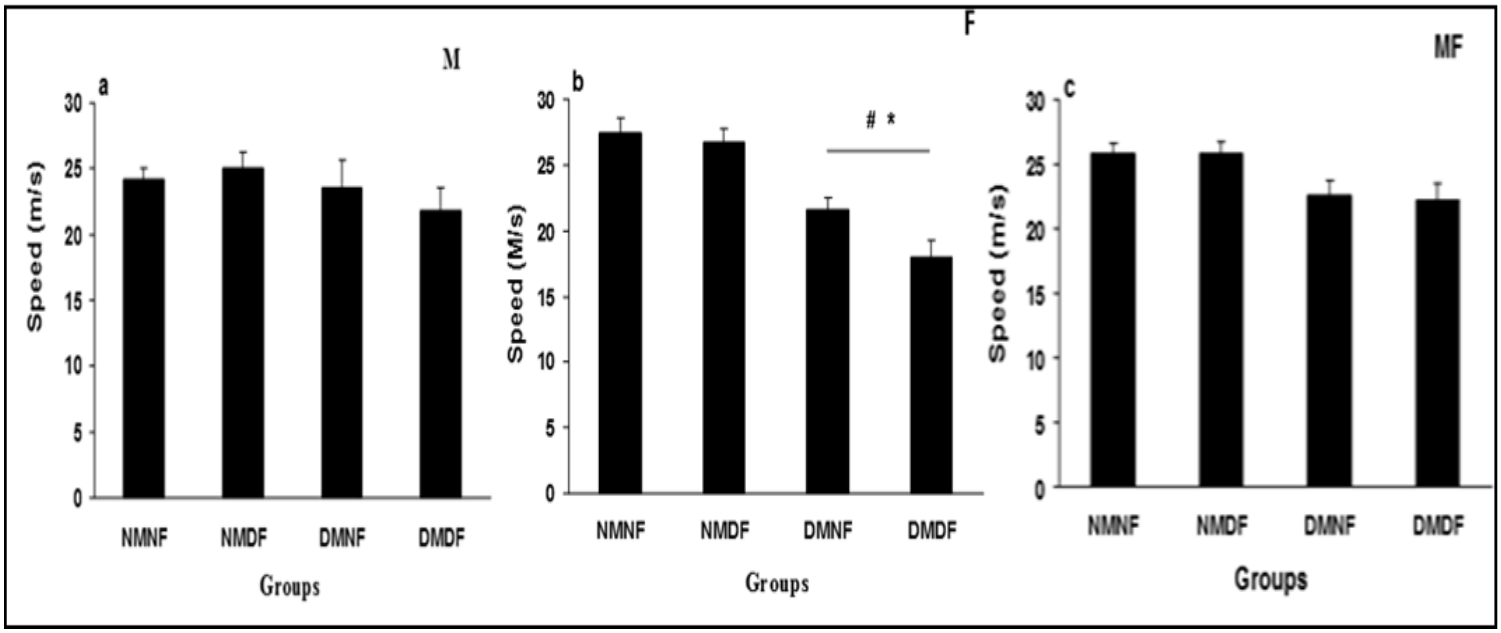

Figure 3: The swimming speed to receive the hidden platform during 4 days spatial training in water maze in male (a), female (b) and total of male and female (c) offspring (* p<.05 vs. NMNF and #P<0.05 vs. NMDF).

Probe trial

As illustrated in figure 4 the percent of total time (seconds) that rats spent in goal quarter (NE, location) during probe trial on the fifth day of test while the platform has been removed was increased significantly in male, female and total of offspring with one diabetic parent (DMNF and NMDF) to compare with NMNF and DMDF offspring group (*P<0.05 vs. NMNF and #P<0.05 vs. DMDF respectively, Fig 4a-c).

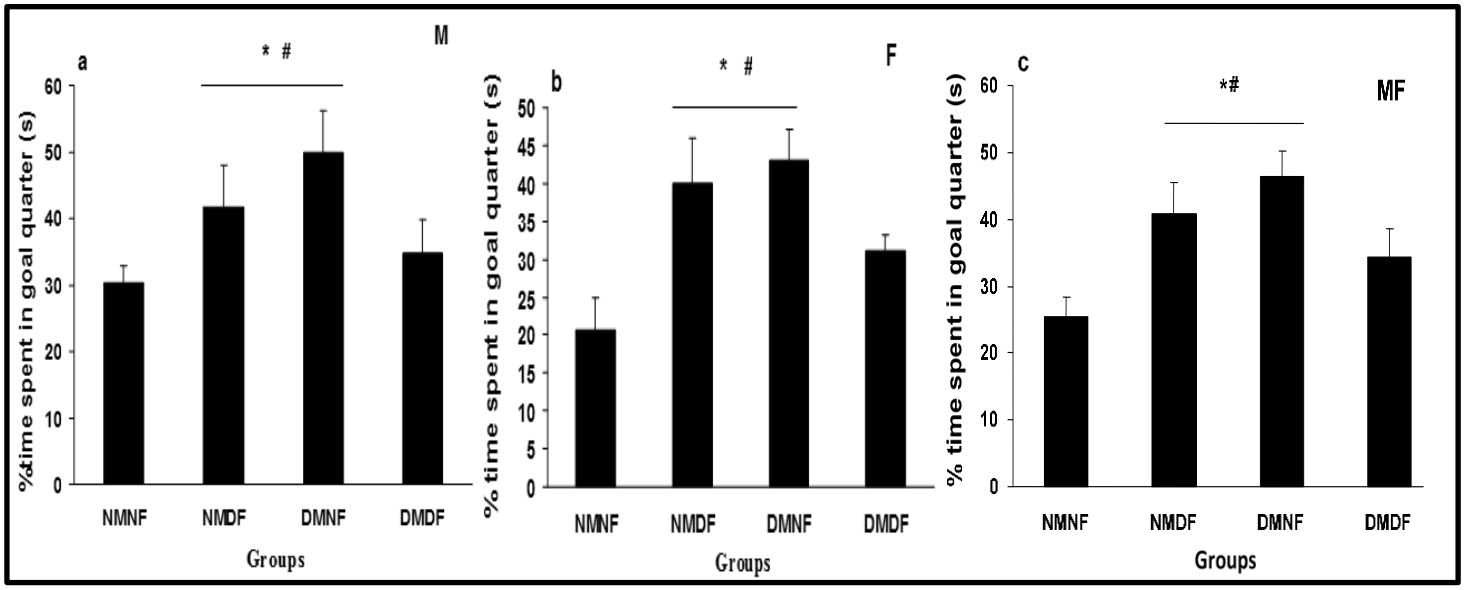

Figure 4: The percent of the total time (seconds) that rats' offspring spent in goal quarter (NE, location) during probe trial on the fifth day of training in water maze. Male (a), female (b) and a total of male and female (c) offspring groups (*P<0.05 vs. NMNF and #P<0.05 vs. NMDF respectively, fig. 4a-c).

Discussion

Our data showed that spatial learning of male offspring of NMDF was impaired; while it increased in female offspring of DMNF group (swimming speed was not changed in both sexes' offspring). Spatial memory of male offspring of DMNF was increased significantly, while in female offspring of both NMDF and DMNF groups (with at least one diabetic parent) was increased significantly.

As many as 10% of pregnancies are complicated by maternal glucose intolerance (Georgieff, 2006). Type -1diabetes in pregnancy can result in significant short- and long-term morbidity to both mother and offspring if management is suboptimal (Bernasko, 2004). It has been reported that alpha-lipoic acid (LA) prevents neural tube defects (NTDs) in offspring of rats with streptozotocin-induced diabetes (Sugimura et al., 2009). Pregnancy in the diabetic woman has long been associated with an increased risk of congenital malformation in the offspring (Kinney et al., 2003). It has been shown that maternal diabetes increases the risk for obesity, glucose intolerance, and Type 2 diabetes mellitus in the adult life of the offspring (Han et al., 2007). Alterations of the intrauterine and early postnatal nutritional, metabolic and hormonal environment may cause a predisposition for disorders and diseases throughout later life. Hormones (such as insulin) in particular are environment-dependent organizers of the developing organism. When they are present in non-physiological concentrations during critical periods of early development, they can dose-dependently lead to a permanent malprogramming of fundamental regulatory systems (Plagemann, 2008).

On the other hand, it has been known that certain pathological conditions that occur during pregnancy, including diabetes, have been linked to abnormal placental morphology and consequent fetal morbidity (Giachini et al., 2008). Some experimental data support the hypothesis that prenatal stress can result in chronic hyperactivity of the hypothalamic-pituitary-adrenal axis, resulting in increased plasma corticosterone concentrations, up-regulation of hepatic gluconeogenesis, and hepatic insulin resistance (Buhl et al., 2007). It has been shown that maternal diabetes increases the risk for obesity, glucose intolerance, and Type 2 diabetes mellitus in the adult life of the offspring (Han et al., 2007), and also maternal malnutrition is known to impair fetal growth and predispose to the development of hypertension and type 2 diabetes. Epidemiological studies have shown strong associations between low birth weight and the incidence of diabetes in the adult offspring (D'Mello A and Liu, 2006).

Recently, studies have demonstrated that intrauterine malnutrition is followed later in male offspring by oxidative stress characterized by increased superoxide generation due to activation of NADPH oxidase and reduced antioxidant defenses (Franco et al., 2007).

Diabetic pregnancy is still associated with an increased rate of congenital malformations despite extensive clinical efforts to

normalize the risk for the offspring. The etiology of diabetic embryopathy is not clear; however, experimental studies have suggested a role for oxidative stress in the teratogenicity of diabetic pregnancy (Cederberg and Eriksson, 2005).

In contrast of some literatures focused on health condition of mother as only important developmental factor in the adult life of the offspring, our results in this work showed that in addition to maternal diabetes that affected the cognition, paternal diabetes also has decreased spatial learning of male offspring while increased spatial learning in the adult life of female offspring. Paternal diabetes same maternal diabetes also has increased the spatial memory of both sexes' offspring. Elevated blood glucose during pregnancy in diabetic mother affects fetus brain development positively at least during fetal life and early postnatal living. The precise biological process behind these effects is not yet completely clarified and remains to more research.

Diabetic pregnancy has a marked influence on offspring calcium and magnesium homeostasis. Urinary excretion of calcium and magnesium is reduced, yet offspring of diabetic pregnancy exhibit hypomagnesemia and hypocalcemia (Bond et al., 2005). Both these conditions can affect cognition by altering the NMDA receptors involving brain neural function.

It is increasingly accepted that alterations of the intrauterine and early postnatal nutritional, metabolic and hormonal environment may predispose individuals to development of diseases in later life. Results from studies of the offspring of diabetic mothers strongly support this hypothesis. It has also been suggested that being light at birth leads to an increased risk of the metabolic syndrome (Syndrome X) in later life (the Barker hypothesis). The pathophysiological mechanisms that underlie this programming are unclear (Plagemann, 2006).

Offspring of women with diabetes are at increased risk for congenital malformations and disturbed growth compared with infants from nondiabetic pregnancies. The precise biological process behind these effects is also not yet completely clarified (Wentzel and Eriksson, 2005). The sex ratio of female vs. male offspring of individuals with Type 1 diabetes did not differ significantly from the expected 1:1 ratio. Compared with the German reference population, individuals with Type 1 diabetes had significantly fewer children and were more often childless. The sex ratio female vs. male offspring of women and men with Type 1 diabetes was unaffected. Maternal history of Type 1 and Type 2 diabetes was associated with a significantly later onset of Type 1 diabetes (Holstein et al., 2012). The effect of family history of type 2 diabetes mellitus (T2DM) on insulin sensitivity and beta-cell function in normoglycemic offspring was investigated. Researchers observed higher BMI, plasma insulin, C-peptide, and pro-insulin and lower insulin sensitivity and beta-cell compensation in normoglycemic offspring of T2DM subjects compared to controls. Differences were greater when both parents and grandparents had T2DM (Praveen et al., 2012).Studies indicate that maternal gestational diabetes (GDM) status is associated with offspring overweight status during childhood. This relationship is only partially mediated by effects on birthweight (Baptiste-Roberts et al., 2012). Glucocorticoids may underlie the association between low birth weight and adult disorders such as hypertension, type 2 diabetes and affective dysfunction. Overexposure to glucocorticoids, especially late in gestation, may explain the link between reduced early growth and adult affective dysfunction (Welberg et al., 2001). No significant differences between diabetic patients and control subjects were found with respect to paternal age, maternal parity, placental weight or any of the birth size parameters, or interventions and complications during delivery (Bache et al., 1999).

Conclusion

It may be concluded that male offspring obtained from paternal diabetes have a risk for spatial learning in adult life at least at an early age, But spatial memory increased significantly in both sexes' offspring generated from paternal or maternal diabetes. The precise biological process behind these effects is not yet completely clarified and little information is available to reveal the mechanisms.

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