Swimming exercise at weaning improves glycemic control and inhibits the onset of monosodium L-glutamate-obesity in mice

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Abstract

Swimming exercises by weaning pups inhibited hypothalamic obesity onset and recovered sympathoadrenal axis activity, but this was not observed when exercise training was applied to young adult mice. However, the mechanisms producing this improved metabolism are still not fully understood. Low-intensity swimming training started at an early age and was undertaken to observe glycemic control in hypothalamic–obese mice produced by neonatal treatment with monosodium L-glutamate (MSG). Whereas MSG and control mice swam for 15 min/day, 3 days a week, from the weaning stage up to 90 days old, sedentary MSG and normal mice did not exercise at all. After 14 h of fasting, animals were killed at 90 days of age. Perigonadal fat accumulation was measured to estimate obesity. Fasting blood glucose and insulin concentrations were also measured. Fresh isolated pancreatic islets were used to test glucose-induced insulin release and total catecholamine from the adrenal glands was measured. Mice were also submitted to intraperitoneal glucose tolerance test. MSG-obese mice showed fasting hyperglycemia, hyperinsulinemia, and glucose intolerance. Severe reduction of adrenal catecholamines content has also been reported. Besides, the inhibition of fat tissue accretion, exercise caused normalization of insulin blood levels and glycemic control. The pancreatic islets of obese mice, with impaired glucose-induced insulin secretion, were recovered after swimming exercises. Adrenal catecholamine content was increased by swimming. Results show that attenuation of MSG-hypothalamic obesity onset is caused, at least in part, by modulation of sympathoadrenal axis activity imposed by early exercise, which may be associated with subsequent glucose metabolism improvement.

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Introduction

Metabolic syndrome increases as obesity becomes a worldwide phenomenon, putting public health authorities on alert. Although a number of different sets of diagnostic criteria have been proposed for this syndrome, it is generally agreed that insulin resistance, hyperglycemia, dyslipidemia, hypertension, and obesity are its five key features (Shaw et al. 2005). The present pandemic is even more serious due to an increase in child metabolic syndrome. Young people may be obese and overweight and even present insulin resistance, hyperinsulinemia, hypertension, and obesity are its five key features (Shaw et al. 2005). The present pandemic is even more serious due to an increase in child metabolic syndrome. Young people may be obese and overweight and even present insulin resistance, hyperinsulinemia, hypertension, and hypercholinesteronemia. Moreover, some even develop non-insulin dependent diabetes mellitus (Weiss & Caprio 2005). Epidemiologic findings indicate that there is a direct correlation between obesity in childhood and metabolic syndrome onset in adult life (Henriksen et al. 1998). Although mechanisms that cause obesity, including early obesity onset, are still obscure, it has been reported that, in obese human beings and experimental animals, metabolic dysfunction may be diagnosed by the deterioration of pancreatic β-cell functions (Prentki & Nolan 2006). β-cell functions are impaired and glucose-induced insulin release is enhanced in obesity, which contributes to hyperinsulinemia (Grassioli et al. 2007). Peripheral insulin resistance in obesity demands an extreme effort of β-cells to produce and release increasing amounts of insulin, which still does not decrease high blood glucose concentration. However, without any improvement in insulin resistance and decreased hyperglycemia, β-cells lose their capacity to regulate insulin secretion and leave high blood glucose levels uncontrolled.

Similar to glucose, other nutrients, such as amino-acids, fatty acids, and their metabolites, also stimulate insulin secretion by pancreatic β-cells. These secretagogues induce an increase in cell metabolism and subsequent ATP production. Potassium ATP sensitive channels (KATP) are inactivated by an increase in ATP/ADP ratio. Membrane depolarization and subsequently the activation of voltage
early exercise and glycemic control on obese mice

Dependent Ca$^{2+}$ channels induce a quick increase in intracellular calcium concentration. High cytosolic free calcium is an intracellular signal that triggers insulin secretion events, even though experimental evidence indicates that glucose may also be stimulating insulin secretion by alternative pathways to K$_{ATP}$ channels (Szollosi et al. 2007). Besides these mechanisms that involve stimulation of the metabolism, β-cells are also subjected to neural control. Pancreatic cells are equipped with several receptors to neurotransmitters and neuropeptides. These receptors are stimulated by efferent signals from the central nervous system (CNS), which includes the autonomic nervous system (ANS) with neural endings at the pancreatic β-cells (Lustig 2003). During glucose blood level oscillations, β-cells receive inputs from the parasympathetic and sympathetic systems to aid glycemia regulation. As a rule, acetylcholine released from parasympathetic ends promotes potentiation of glucose-induced insulin secretion, whereas noradrenaline, released from sympathetic terminals, and adrenaline secreted from adrenomedullary cells inhibit it (Ahren et al. 2006). It has been observed that neural control of insulin secretion and glycemia is damaged in obesity (Jeanrenaud 1986). ANS imbalance has been reported in obese human beings and in rodents (Atéf et al. 1992, Leigh et al. 1992, Weyer et al. 2001). Fasting hyperinsulinemia in obesity is related to insulin oversecretion, which is partially attributed to high parasympathetic activity, while sympathetic tonus decreases (Bray 1991, Lucinei Balbo et al. 2000, Balbo et al. 2002).

Administration of monosodium l-glutamate (MSG) to suckling rodent pups kills neurons in hypothalamic areas and induces changes in CNS development (Semprini et al. 1974, Xu et al. 2007). Adult MSG rats and mice actually show disturbances in body weight control, which lead to an increase in adiposity, hyperinsulinemia, and insulin resistance (Machado et al. 1993, Lucinei Balbo et al. 2000, Macho et al. 2000, Maletinska et al. 2006). Unlike other obese rodents, such as those from a different genetic origin or with CNS lesions, overeating in MSG-rodents does not occur (Brayman et al. 1992, Martins et al. 2001). While adult (90-day-old) MSG rats are normoglycemic, neonatal MSG adult mice have hyperglycemia (Lucinei Balbo et al. 2000, Grassioli et al. 2007). Insulin oversecretion and altered ANS activity have been registered in these MSG-obese rodents (Lucinei Balbo et al. 2000, Balbo et al. 2002) and in other obese animal models (Campfield et al. 1986, Jeanrenaud 1986, Mitrani et al. 2007). It has also been shown in our laboratory that MSG-obese mice also have high parasympathetic input and impairment in sympathoadrenal axis activity. Their chromaffin adrenal cells release low amounts of catecholamines and their biosynthesis is reduced (Lucinei Balbo et al. 2000, Martins et al. 2001, 2004, Balbo et al. 2002).

It has been shown recently by our laboratory that a low-intensity swimming program, started at the weaning period, is able to reestablish the catecholamine production on adrenal medullary cells and inhibit MSG-obesity onset in adult mice (Scomparin et al. 2006). Human beings and animals with metabolic syndrome undergoing physical exercises improved their blood insulin and glucose levels (Scheurink et al. 1992, Sherman et al. 1993, Ross et al. 2004). Nevertheless, with regard to the benefit of physical exercises, the mechanisms involved in the improvement of metabolism are still debated. At least in part, the stimulation of sympathoadrenal axis activity may be one of the factors involved (Scomparin et al. 2006). The effect of physical exercises on metabolism is blocked in lean rats with adrenal demedullation (Henriksson et al. 1985). A low-intensity swimming program in 60-day-old mice, for 30 days, is unable to restore sympathoadrenal catecholamine stocks and inhibit MSG-obesity onset, as occurs when exercises start on the 21st day of birth, on weaning (Scomparin et al. 2006). Present work verifies whether, besides reducing fat tissue accumulation, low-intensity swimming in MSG-weaned mice also protects them from metabolic disturbance and impaired glucose-induced insulin secretion.

Materials and Methods

Animals

All animal protocols were approved by the Ethics Committee of the State University of Maringá. Sets were formed from two female mice mated with one male Swiss mouse, all 60 days old. After 1 week the pregnant mice were separated. On delivery, the litter size was corrected to six to assure milk amount to all pups (Moura et al. 1996). During the first 5 days after birth, MSG (4 mg/g body weight) was injected s.c. in the pup’s cervical area. Control animals were injected with a saline solution. The day before weaning (21st day), males were selected and all females were discharged. Control and MSG mice were randomly chosen for exercise. Animals received water and commercial chow (Nuvital, Curitiba, Brazil) ad libitum and placed in an environmentally controlled room (23±3°C and 12 h light:12 h darkness photocyte (07:00–19:00 h)) during the whole protocol period.

Swimming training

Control and MSG-obese mice were trained by free swimming in a glass tank (30×35×30 cm), filled with tap water at 32±3°C. Mice swim over a period of 8 weeks (EXE), for 15 min a day, 3 days a week. Six mice from each group were placed simultaneously into the pool at 17:00. A lead weight, corresponding to 2.5% of their body weight, was attached on the tip of their tails to ensure that animals were in constant swimming activity. Two groups, control and MSG, of sedentary mice (SED), aged 21–90 days old, did not swim at all. The swimming program should be considered a light exercise when compared with the moderate training program in which mice freely swim for 60 min, 5 days a week, for 18 weeks (Napoli et al. 2004). After each exercise session, mice were dried with paper towels and returned to their respective boxes until the next swimming session.

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**Obesity**

To evaluate obesity onset, all 90-day-old mice, trained or untrained, were anaesthetized by an i.p. injection of sodium pentobarbital (5 mg/100 g body weight) and killed by cervical dislocation. Perirenal adipose fat pads were removed, washed, and weighed to estimate obesity induced by MSG treatment (Scomparin et al. 2006).

**Food intake**

After weaning, mice from all groups were weighed and food intake determined every week by non-ingested chow. Food intake was calculated by chow consumed divided by body weight from each animal. Total area under the curve of food consumption versus time was calculated (Martins et al. 2001).

**Adrenal glands**

Adrenal glands were removed and weighed. During handling, glands were maintained in standard Krebs–Hepes solution on an ice bath. The total of adrenal gland catecholamines – epinephrine and norepinephrine – was quantified by employing the trihydroxyindole fluorescence method (Kelner et al. 1985). The parameters used in the fluorometer were 420 nm for excitation and 510 nm for emission. For total tissue catecholamine content, right and left glands were homogenized in 350 μl of 10% acetic acid using an ultrasonic processor and centrifuged at 10 000 g for 1 min. Results were obtained by plotting the values on a linear regression of the standard epinephrine curve.

**Glycemia and insulinemia**

Total blood was collected after 14 h fasting to measure plasma glucose and insulin concentration by glucose-oxidase technique (Kit-Bio Diagnostic Chemistry Industry, Paraná, Brazil) and RIA (Hermans et al. 1987) respectively.

**Intraperitoneal glucose tolerance test**

Intraperitoneal glucose tolerance test (ipGTT) was performed by injecting glucose (2 g/kg body weight) i.p. in overnight-fasted mice. Blood glucose levels were determined prior to injection and 30, 60, 90, and 120 min after injection. Blood samples were obtained from the tail vein and plasmas used to measure glucose concentration by the glucose oxidase method. The total area under the curve of ipGTT was calculated.

**Determination of homeostasis model assessment of insulin resistance**

The homeostasis model assessment of insulin resistance (HOMA-IR) was calculated by glucose and insulin determinations obtained after 14 h of chow withdrawal, using the formula: fasting glucose (mmol/l) X fasting insulin (mU/ml)/22.5. HOMA has been used as an estimating index of tissue sensitivity to insulin action in human beings and rodents, mice included (Bonora et al. 2000, Konrad et al. 2007).

**Insulin tolerance test**

Insulin tolerance test (ITT) was performed with another mice batch, MSG-treated and untreated SED an EXE, fasted overnight, underwent an i.p. insulin infusion (1 U/kg body weight of insulin), and samples for blood glucose measurements were collected at 0 (basal), 5, 15, 30, and 45 min after injection. Thereafter, the rate constant for plasma glucose disappearance (Kint) was calculated by formula 0.693/(t1/2), as indicated in a previous report. The plasma glucose t1/2 was calculated from the slope of the least square analysis of the plasma glucose concentrations during the linear phase of decline (Hirata et al. 2003).

**Glucose-induced insulin release in pancreatic islets**

Collagenase technique (Lacy & Kostianovsky 1967), with modifications, was employed to isolate pancreatic islets as previously described. Intact mice from all groups were deeply anesthetized with sodium pentobarbital (5 mg/100 g body weight). The abdominal wall was cut and opened; whole pancreas was isolated, washed with Hank's buffered saline solution (HBSS), weighed, and quickly chopped. Supernatant solution was discharged after precipitation of pieces of pancreas. Suspension was incubated with HBSS containing collagenase type IV (0.5 mg/ml pancreas pieces suspension, Sigma Chemical CO.), at 37 °C, for 10 min. Suspension was then filtered with a 0.5 mm metal mesh and washed with HBSS, containing 0-12% BSA fraction V in five continuous washings. Islets were collected with the aid of a microscope. Groups of four islets placed on plastic cover slips were pre-incubated for 60 min in 1-0 ml of Krebs–Ringer bicarbonate-buffered solution containing 0-12% (wt/vol) BSA (fraction V), and glucose 5-6 mM, pH 7-4. The solution was equilibrated against a mixture of CO₂ (5%) and O₂ (95%). After adaptation to low glucose concentration solution, islets were incubated for a further 60 min in glucose 5-6 and 16-7 with Krebs–Ringer solutions. Islets used to observe insulin secretion were obtained from at least ten different mice in each experimental group. Aliquots from incubations were used to measure insulin concentration by RIA.

**Chemicals**

To use in RIA, human recombinant insulin marked with I125 was acquired from Pharmacia. Routine reagents were purchased from Sigma, unless and otherwise specified.

**Statistical analysis**

All results are presented as mean ± s.e.m. P<0.05 was considered statistically significant. One-way ANOVA with
Bonferroni post-test and Student’s *t*-test were performed using GraphPad Prism version 5.00 for Windows (GraphPad Software, San Diego, CA, USA).

**Results**

As shown in Fig. 1 (left panel), MSG treatment induced 45.9% enhancement of periepididymal fat pad when compared with that of control animals (*P*<0.001). Swimming exercises, started on the 21st day of age, reduced fat tissue of 90-day-old MSG mice by 36.1% when compared with non-swimming ones (*P*<0.001). Furthermore, exercises reduced fat tissue in control mice by 34.1%. Figure 1 also shows (middle and right panel) that MSG treatment induced increases of 48.7 and 148.2% in glucose and insulin blood concentration respectively, when rates were compared with the sedentary control group (*P*<0.001). However, swimming eliminated fasting hyperglycemia and hyperinsulinemia. Exercise did not change glucose and insulin blood levels in control mice.

Mice from all groups responded to glucose load during ipGTT with an increase in transient blood glucose concentration (Fig. 2, upper panel). MSG-sedentary animals had higher glycemia than control mice. At the end of the test, there was a 45% rise in blood glucose levels in sedentary MSG mice compared with fasting control mice (*P*<0.001). In the case of MSG mice, swimming reduced the transient rise in glucose level to the same concentrations in control animals. No alterations were registered in control mice which underwent exercise. Calculating the area under the curve of blood glucose concentration throughout ipGTT, sedentary MSG mice showed a 43.4% increase when compared with controls, *P*<0.001 (Fig. 2, lower panel). Swimming completely restored the glycemic levels in MSG mice when these levels are compared with those of controls. Exercise in normal mice did not alter blood glucose concentration during ipGTT.

Figure 3 shows that MSG-obese mice presented a 4.2-fold increase in HOMA-IR, *P*<0.001. Exercises did not change this index in control mice. However, swimming decreased HOMA-IR in exercised MSG mice, which reached the same rate as that in control mice with or without exercise.

Figure 4 shows that MSG obese animals present 60.5% decrease in insulin sensitivity, using the *K*<sub>itt</sub>; however, the exercise increase *K*<sub>itt</sub> in 197.8%, *P*<0.05. Insulin sensitivity was also raised on lean mice exercise, as showed an increase of 51.5% in their *K*<sub>itt</sub>. Figure 5 shows not only that MSG treatment did not change chow consumption, but also that the swimming program failed to cause any alteration in food intake in MSG or control mice.
At low concentration, or rather, 5.6 mM, glucose stimulated insulin release in islets from control as well as from MSG mice. However, a 2.55-fold increase was reported in insulin secretion in islets from sedentary MSG mice when compared with that in controls \( (P < 0.001) \). Although exercise did not cause any changes to MSG mice in insulin secretion induced by 5.6 mM of glucose, swimming control animals secreted 2.11 times more than sedentary ones \( (P < 0.001) \). When glucose concentration was increased from 5.6 to 16.7 mM, islets responded by secreting more insulin, increasing 3.87 times in sedentary MSG mice and 2.84 times in control mice, \( P < 0.001 \) (Fig. 6, right panel).

Insulin secretion, stimulated by 16.7 mM of glucose to islets from exercised MSG mice, shows a 1.6-fold increase when compared with the rate in sedentary mice. Nevertheless, islets from exercised MSG mice secreted 1.83 times more insulin than MSG sedentary ones \( (P < 0.001) \). In exercising mice insulin secretion rose by 2.6 times for controls and 5.0 times for MSG mice when glucose levels rose, \( P < 0.001 \) (Fig. 6).

Figure 7 shows total catecholamine stores in adrenal glands of mice. Neonatal treatment with MSG caused a 43.8% reduction in catecholamine contents of the adrenal glands when compared with those in control mice \( (P < 0.001) \). However, MSG mice submitted to swimming after weaning, increased their catecholamine storage by 57.5% when compared with that of sedentary MSG mice \( (P < 0.001) \). Exercise caused a 44.1% catecholamine increase in control animals \( (P < 0.001) \). Exercised MSG mice reached the same values of catecholamine content observed in untrained control mice.

Discussion

Neonatal treatment with MSG causes fasting hyperinsulinemia in adult rodents; however, hyperglycemia is observed only in MSG mice (Lucinei Balbo et al. 2000, Macho et al. 2000, Balbo et al. 2002). In this research, hyperinsulinemia coupled to high blood glucose concentration is reported in MSG mice. MSG treatment provokes lesions in a significant number of neurons in the hypothalamic arcuate nucleus (ARC) and thus a disarrangement of an important area involved in body weight (Olney 1969) and glycemic control (Schwartz & Porte 2005). Obese hyperinsulinemic rodents, with a genetic defect related to the ARC function, such as Zucker rats, and ob/ob and db/db mice, manifested hyperphagia (Olney 1969, Brayman et al. 1992). However, present data show that MSG mice do not increase food intake, corroborating previous literature (Dawson et al. 1989, Balbo et al. 2000). Although MSG mice manifest normophagia, increased fat is accumulated in their periepididymal pads. This fat accumulation characterizes obesity, as present research and literature by other authors demonstrate (Olney 1969, Maletinska et al. 2006, Scomparin et al. 2006). The swimming program used did not disturb food intake of MSG or of control mice. Data confirm the fact that physical exercise does not change food intake (Irani et al. 2005).

Although no decrease in food consumption was reported, exercise training caused a decrease in fat tissue accumulation in the two animal groups. However, fat reduction reported in exercised MSG mice may be compared with fat accumulation...
at similar levels in normal sedentary mice. In spite of the fact that the data above suggest that the swimming program is able to inhibit MSG-obesity onset, one may not conclude that this kind of exercise causes complete blocking of obesity onset, since exercise also significantly reduces fat accumulation in control mice. It has been observed that 90-day-old adult MSG mice which swim after weaning for 30 or 70 days presented less fat accretion than sedentary MSG mice or those which only started swimming at 60 days of age (Scomparin et al. 2006). Recently, similar results were found, juvenile weaning rats selected to develop diet-induced obesity when submitted to exercise training, showed significative inhibition of genetic tendency to develop obesity. When voluntary running was halted rats continued to resist gaining body weight (Patterson et al. 2008).

The swimming program also normalized blood insulin levels in MSG mice. Hyperinsulninemic human beings and rodents submitted to different types of exercises show reduction of blood insulin levels, even though the decrease rate depends on duration and intensity of training (Torgan et al. 1993, Kretschmer et al. 2005). It has been suggested that decrease in fat tissue accumulation is related to normalization of fasting insulin levels and, it is well known, insulin has been identified as an adiposity signal, like leptin (Schwartz & Porte 2005). Increases in fasting blood insulin concentration follow rises in fat tissue contents (McMinn et al. 2000). As has been shown in MSG mice, fasting hyperinsulinemia may also be caused or aggravated by a failure in tissue insulin action, which leads to peripheral insulin resistance (McMinn et al. 2000). HOMA-IR used as a tissue insulin sensitivity index (Bonora et al. 2000, Konrad et al. 2007), shows that MSG-obese mice are insulin-resistant. While HOMA-IR is an insulin sensitivity index controversial to rodents, our results obtained with constant for plasma glucose disappearance ($K_{ig}$) confirm that MSG-obese mice are insulin resistant (Hirata et al. 2003) and exercise improved insulin sensitivity. A decrease in the stimulatory effects of insulin on glucose transport in adipocytes from MSG rats has been demonstrated (Macho et al. 2000). MSG rodents have lower contents of glucose transporter (GLUT4) protein in their fat cells, skeletal, and cardiac muscles, and in the brown adipose tissue (Machado et al. 1993, Papa et al. 1997). However, since GLUT4 contents increased in the white adipose tissue during the development of obesity in MSG mice, they may still have a key role in fat tissue accumulation recorded in MSG mice (de Carvalho Papa et al. 2002). Swimming completely restored the tissue insulin sensitivity in MSG mice. Although other exercises by hyperinsulinemic human beings and rodents induce improvements in insulin resistance, degree of exercise effects depends on duration, frequency, and intensity of exercise (Becker-Zimmermann et al. 1982, Walberg et al. 1984, Houmard et al. 2004). Physical activity may reduce insulin resistance and improve glucose intolerance in obese human beings and animals (Hahn et al. 1999, Okada et al. 2004). A single bout of exercise increases the rate of glucose uptake into the contracting skeletal muscles, a process that is regulated by the translocation of GLUT4 to the plasma membrane (Goodyear & Kahn 1998). Furthermore, exercise training increases GLUT4 protein in muscle (Torgan et al. 1993). Exercise and insulin utilize different signaling pathways and both allow activation of glucose transport. The above may explain why human beings and experimental animals with insulin resistance may increase muscle glucose transport in response to an acute bout of exercise (Hayashi et al. 1997). Ca$^{2+}$ release from the sarcoplasmic reticulum is a mechanism that affects the insulin-independent pathway by which muscle contractions stimulate glucose transport. Another mechanism involves AMP-activated protein kinase (Racette et al. 2005). The swimming program is able to normalize fasting glycemia and improve glucose tolerance of MSG mice. Although these data indicate that glucose uptake on peripheral tissues is activated by exercises, this effect may not be only due to the insulin-independent pathway since exercises also reduce insulin levels and fat tissue storage. This fact corroborates the involvement of an increase in insulin tissue sensitivity. Actually, HOMA-IR and $K_{ig}$ from exercised MSG mice is similar to that in untrained control mice.

![Figure 5](image_url) Effect of MSG treatment and swimming on food intake. Bars represent mean of food consumption for 10–12 animals in each group. Lines at top of bars represent S.E.M.

![Figure 6](image_url) Effect of MSG treatment and swimming on insulin secretion stimulated by low (5.6 mM) and high (16.7 mM) glucose concentration. Islets were obtained from a pool of 10 mice for each group. Bars represent mean of 20–40 batches of islets. Lines at top of bars represent S.E.M. Letters over bars represent significant differences with P<0.05 between groups: (a) control SED; (b) control EXE; (c) MSG SED, and (d) MSG EXE. *Represents significant differences between insulin secretion induced by 5.6–16.7 mM for each group.
Figure 7 Effect of MSG treatment and swimming on total catecholamine content from adrenal medullae. Bars represent mean catecholamine content from adrenal medullae isolated from 10 to 12 animals in each group. Lines at the top of bars represent S.E.M. Letters over bars represent significant differences with $P<0.05$ between groups: (a) control SED; (b) control EXE; (c) MSG SED, and (d) MSG EXE.

There have been several experiments producing evidence that MSG rodents present low sympathetic activity (Yoshida et al. 1990, Bray 1991, Scomparin et al. 2006). Studies in our laboratory have shown reduced secretory capacity of adrenal medullar chromaffin cells from MSG mice, coupled to low catecholamine stores and reduced expression of tyrosine hydroxylase (TH), a limiting enzyme to catecholamine biosynthesis (Martins et al. 2001, 2004). Whereas acute and long term exercises stimulate sympathetic driving, blood levels of catecholamine and its turnover are increased by exercise (Stallknecht et al. 1996). A low-intensity swimming program started at weaning reestablishes the catecholamine production on adrenal medulla cells and inhibits the MSG-obesity onset in adult mice (Scomparin et al. 2006). In results not shown in the present paper, the same exercise protocol was able to enhance the TH protein expression in MSG mice. Since present research has also shown that exercises recovered catecholamine contents from adrenal medullae isolated from MSG mice, this fact may have contributed to the inhibition in vivo of insulin over-secretion and to restore normoinsulinemia. Epinephrine, released from adrenal medulla, and noradrenaline released from the sympathetic nerve endings, inhibit insulin release via stimulation of $\alpha_{2}$-adrenergic receptors on the $\beta$-cells of Langerhans islets (Mitrani et al. 2007). In addition, long term (12 weeks) swimming exercises applied to adenoremedullated lean rats do not improve glycemic homeostasis (Henriksson et al. 1985). However, it has also been observed that adenoremedullated rats submitted to voluntary running improve in tissue insulin sensitivity (Okada et al. 2004).

Experiments in our laboratory (Lucinei Balbo et al. 2000) have shown that islets from MSG mice increased overall insulin secretion 14 times, from 5.6 to 16.7 nM glucose perfusion, while islets from control mice increased 28 times. Low secretion in response to high glucose concentration may indicate dysfunction in pancreatic $\beta$-cells, which may lead to development of type 2 diabetes in obese mice (Nagata et al. 2006). Present research also observes failure in insulin secretion control of $\beta$-cells from MSG mice. In fact, the insulinotropic effect of high glucose concentration is decreased in MSG-obese mice when compared with that in lean ones. Exercises induce an increase in insulin release in islets from MSG mice, stimulated by the high glucose dose, which is greater than that in lean mice. Results indicate that the swimming program preserves the ability of pancreatic $\beta$-cells from MSG mice to respond to glucose concentration changes in a controlled manner. This occurs in spite of the fact that in vivo pancreatic islets are submitted to many factors that modulate the insulin-release process, which include parasympathetic and sympathetic inputs. Exaggerated fasting insulin levels and glucose intolerance of MSG-obese mice are corrected by swimming. The above suggests that the sympathetic drive may contribute towards reduced insulin blood concentration.

In conclusion, results show that light swimming, started at weaning, considerably inhibits the obesity onset induced by neonatal treatment with MSG in mice. Effects of exercises are related to sympathoadrenal axis activity. Exercises may also abolish hyperglycemia. Insulin secretion control and tissue insulin sensitivity are protected by exercise against deterioration observed in MSG-obese sedentary mice. We suggest that light exercises, applied at an early age to MSG mice, may interfere in the central control of energy expenditure, which preserves tissue insulin sensitivity and $\beta$-cell insulin secretion control. Insulin secretion and tissue insulin sensitivity preserved by this exercise program could suggest a way to protect against type 2 diabetes onset; however, further studies must be undertaken to clarify these mechanisms.

Declaration of interest

Authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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