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Original Research

Blunted renal dopaminergic system in a mouse model of diet-induced obesity

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Abstract

Obesity has reached epidemic proportions in the Western world and is implicated in the pathophysiology of essential hypertension. The aim of the present study was to evaluate sodium handling, blood pressure and renal dopaminergic system activity in a mouse model of obesity induced by exposure to a hypercaloric diet. From six to 18 weeks of age, animals were fed with a control diet or a high-fat high-simple-carbohydrate (HFHSC) diet. Renal function, blood pressure and urinary and plasmatic catecholamines and biochemical parameters were evaluated in both groups. In parallel, the effects of high sodium intake (HS, 1.0% NaCl, 3 days) on natriuresis, urinary catecholamine excretion and aromatic L-amino acid decarboxylase (AADC) activity were evaluated in control and obese mice. Mice exposed to the HFHSC diet presented obesity, hyperglycemia, glucose intolerance, insulin resistance, hyperinsulinemia and increased blood pressure. This was accompanied, in obese mice, by decreases in urinary excretion of dopamine and metabolites as well as reduced AADC activity in renal tissues. During HS intake, absolute urinary dopamine excretion increased in control, but not in obese mice. This was accompanied in obese mice by a natriuretic resistance on day 1 of the HS diet. In addition, obese mice presented increased urinary and plasmatic noradrenaline levels, as well as an increased heart rate when compared with control mice. In conclusion, in this model of diet-induced obesity hyperinsulinemia, insulin resistance and increased sympathetic tone are associated with blunted renal dopaminergic activity. It is suggested that this may contribute to compromised sodium excretion and increased blood pressure in obesity.

Keywords: kidney, dopamine, noradrenaline, obesity, blood pressure and natriuresis

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Introduction

At the level of the proximal tubule, an overall increase in sodium excretion is produced by dopamine and D_1-like receptor agonists, which results from the inhibition of several sodium transporters, including Na^+/K^+-ATPase[1] and Na^+-H^+ exchanger,[2] at the basolateral and apical membranes, respectively. In fact, during moderate salt intake, renal dopamine, as a result of D_1-like receptor activation, is responsible for ~50% of the sodium excretion.[3–5] Tubular proximal epithelial cells are endowed with a high aromatic L-amino acid decarboxylase (AADC) activity, the enzyme responsible for the conversion of circulating or filtered L-3,4-dihydroxyphenylalanine (L-DOPA) to dopamine.[6,7] Dopamine of renal origin has also been found to undergo inactivation by extensive deamination to 3,4-dihydroxyphenylacetic acid (DOPAC) through type A and B monoamine-oxidase (MAO-A and MAO-B), *O*-methylation to 3-metoxytyramine (3-MT) through catechol-*O*-methyltransferase (COMT) and deamination plus *O*-methylation to homovanillic acid (HVA) through MAO-A, MAO-B and COMT.[8,9]

Adrenergic receptors exist on most nephron segments, indicating that renal cells are under some degree of control by the adrenergic system.[10,11] Thus, noradrenaline released from renal sympathetic nerve terminals or reaching the kidney from the circulation may modulate salt and fluid transport.[10,11] In fact, noradrenaline was suggested to

promote renal sodium reabsorption in proximal convoluted tubules by increasing Na^+/K^+-ATPase activity[12] and NHE-3 protein abundance.[13]

Dopamine and norepinephrine exert opposite effects on tubular sodium reabsorption, with dopamine acting as a natriuretic factor and noradrenaline as an anti-natriuretic factor.[10] Indeed, dopamine and noradrenaline control Na^+/K^+-ATPase activity by exerting opposing effects on a common intracellular signaling system of second messengers, protein kinases and protein phosphatases, ultimately determining the phosphorylation state of Na^+/K^+-ATPase activity.[10]

Obesity has reached epidemic proportions in the Western world[14] and associates with an array of metabolic and cardiovascular complications. Namely, obesity has been increasingly implicated in the pathophysiology of essential hypertension, although the mechanisms by which excessive weight raises blood pressure remain largely undefined. However, it has been already shown that obesity is associated with increased proximal tubular sodium reabsorption,[15–17] salt retention and increase in systemic arterial pressure.[18] A diminished natriuretic response to D_1 receptor activation was observed in Zucker fatty rats[19] and in Wistar fatty rats.[20] Moreover, animal models of obesity (Wistar fatty rats), as well as metabolic syndrome patients, present sympathetic hyperactivity.[20–22]

However, obesity in these models (Zucker fatty rats and Wistar fatty rats) is due to leptin receptor gene mutation which is responsible for leptin signaling deficiency.[23] However, leptin abnormalities only comprise a minority of obesity cases in humans.[24] On the other hand, polygenic models of obesity may provide more insight into the human condition since human obesity is most likely mediated by multiple genes.[23] C57BL/6J mice are most widely used for diet-induced obesity because they exhibit abnormalities similar to human metabolic syndrome when fed with a high-fat high-simple-carbohydrate (HFHSC) diet.[25]

C57BL/6 mice fed with a HFHSC diet have been previously shown to present obesity, sympathetic hyperactivity and hypertension.[26–28] The aim of the present study was to evaluate, for the first time, renal dopaminergic system activity in this mouse model of diet-induced obesity.

Materials and methods

In vivo studies

Animals: All *in vivo* investigations were performed in accordance with the European Directive number 86/609, transposed to the Portuguese Law by DL 129/92 and by Portaria 1005/92. Five-week-old normotensive male C57BL/6J mice (Charles River, Barcelona, Spain), were selected after a seven-day period of stabilization and adaptation to blood pressure measurements. The animals were kept under controlled environmental conditions (12:12 h light/dark cycle and room temperature $22 \pm 2^{\circ}C$).

Obesity mouse model: Six- to eighteen-week-old animals were fed *ad libitum* for 12 weeks with a control diet (Teklad LM-485 Mouse/Rat Sterilizable Diet; Madison, WI, USA) – control mice, or a HFHSC diet (F2685 Diet; BioServe, Frenchtown, NJ, USA) – obese mice. Body weight, water intake and food consumption were monitored weekly throughout the study.

Blood pressure measurements: Blood pressure (systolic and diastolic) and heart rate were measured weekly throughout the 12-week period in conscious restrained animals, in a temperature control box at 37–38°C, using a photoelectric tail-cuff pulse detector (LE 5000; Letica, Barcelona, Spain). Four determinations were made each time and the means were used for further analysis.

Glucose tolerance and insulin resistance tests: Eleven weeks after control or HFHSC diet intake, glucose tolerance and insulin resistance tests were performed. Glucose tolerance tests were carried out after 14 h fast through a single dextrose injection (1.0 g/kg body weight [bw], intraperitoneally). Blood glucose concentration was measured before and 15, 30, 45, 60, 90 and 120 min after injection using a blood glucose meter (Freestyle Mini™ system; Abbott Diabetes, Mississauga, ON Canada). Insulin resistance tests were carried out after a 6-hour fast through a single injection of insulin (1.5 U/kg bw, intraperitoneally). Blood glucose concentration was measured before and 15, 30, 45 and 60 min after injection using a blood glucose meter (Freestyle Mini™ system; Abbott Diabetes).

Metabolic study: Twelve weeks after control or HFHSC diet intake, the animals were placed in metabolic cages (Tecniplast, Buguggiate-VA, Italy), and submitted to a normal or high sodium intake (HS, 1.0% NaCl w/v) in their drinking water during three days, for collection of 24-h urine for later determinations of sodium, creatinine and catecholamines. The vials for collecting urine for quantification of catecholamines contained 60 μL of hydrochloric acid (6 mol/L) to avoid spontaneous oxidation of the amines and its derivatives. At the end of the metabolic study, the animals were anesthetized with pentobarbital sodium (50 mg/kg bw; intraperitoneally) and blood was collected from the heart in tubes containing heparin and lithium/heparin for later determination of plasma catecholamines and biochemical parameters, respectively. The kidneys were rapidly removed and weighed. The outer cortex was isolated and fragments were used for latter determination of AADC, COMT, MAO-A and MAO-B activities. Other fragments from renal cortex weighing around 100 mg were placed in vials containing 0.5 mL of perchloric acid 0.2 mol/L and stored at −80°C for later catecholamine and metabolite quantification, by high-performance liquid chromatography (HPLC) with electrochemical detection. The right gonadal fat pad was also weighted, and the proportional weight of the gonadal fat pad was used as an estimate of total body fat, as previously described.[27]

In vitro studies

Assay of catecholamines: The assay of catecholamines and its metabolites in urine, plasma and renal tissues was performed by HPLC with electrochemical detection, as previously described.[29] In our laboratory, the lower limit of

Table 1 Body and kidney weight, metabolic balance, renal function and blood pressure in control and obese mice

	Control	Obese
Body weight (g)	25.2 ± 0.4	37.3 ± 2.0*
PWGFP (% g/g)	0.68 ± 0.04	2.51 ± 0.13*
Kidney weight (g)	0.32 ± 0.01	0.33 ± 0.01
Plasma glucose (mg/dL)	144.6 ± 8.1	166.8 ± 7.3*
Plasma insulin (ng/mL)	0.62 ± 0.04	1.02 ± 0.16*
Plasma cholesterol (mg/dL)	74.5 ± 2.4	82.4 ± 2.4*
Plasma triglycerides (mg/dL)	25.1 ± 2.0	36.3 ± 1.8*
Plasma Na^+ (mmol/L)	138.0 ± 2.2	138.6 ± 2.7
Urine Na^+ (mmol/day)	0.18 ± 0.03	0.17 ± 0.03
FE_{Na^+} (%)	1.34 ± 0.37	1.03 ± 0.33
Ccreat (mL/min)	0.09 ± 0.03	0.12 ± 0.03
Heart rate (bpm)	429 ± 4	463 ± 6*
Systolic blood pressure (mmHg)	135 ± 2	158 ± 2*
Diastolic blood pressure (mmHg)	95 ± 1	119 ± 2*

Ccreat, creatinine clearance; FE, fractional excretion; PWGFP, proportional weight of the right gonadal fat pad
Values are mean ± SE; $n = 6$ to 8 experiments per group
*Significantly different from values in control mice ($P < 0.05$)

detection of dopamine and dopamine metabolites (DOPAC, 3-MT and HVA) and noradrenaline ranged from 350 to 1000 fmol.

Plasma and urine ionogram and biochemistry: In plasma and urine samples, the quantification of sodium was performed by ion-selective electrodes and creatinine by the Jaffé method through a Cobas Mira Plus analyser (ABX Diagnostics, Geneva, Switzerland). Creatinine clearance and fractional excretion of sodium were calculated as previously described.[30] In plasma samples, the quantification of cholesterol was performed by selective inhibition colorimetric assay and the quantification of triglycerides was performed by an enzymatic colorimetric test, GPO/PAP method also through the Cobas Mira Plus analyser (ABX Diagnostics). Serum insulin was quantified by enzyme-linked immunosorbent assay, according to the manufacturer's instructions (Linco Research, St Charles, MO, USA).

AADC activity: The AADC activity was determined in fragments of renal cortex as previously described[31] using L-Dopa as substrate (100–10,000 μmol/L). The assay of dopamine was performed by HPLC with electrochemical detection. The protein content in cell suspension (1.5 mg/mL) was determined by the Bradford method.[32]

COMT activity: COMT activity was evaluated by the ability of fragments of renal cortex to methylate adrenaline (3–1000 μmol/L) to metanephrine, as previously described.[30] The assay of metanephrine was performed by HPLC with electrochemical detection. The protein content in cell suspension (1.5 mg/mL) was determined by the Bradford method.[32]

MAO activity: MAO activity was determined in fragments of renal cortex, as previously described.[30] MAO activity was determined with [^{3}H]-5-hydroxytryptamine (5-HT, 2–400 μmol/L) as a preferential substrate for MAO-A and [^{14}C]-β-phenylethylamine (β-PEA, 0.25–50 μmol/L) as a preferential substrate for MAO-B. The deaminated products were extracted with ethyl acetate and measured by liquid scintillation counting.

Drugs: The compounds dextrose, DOPAC, dopamine hydrochloride, HVA, L-Dopa, metanephrine, 3-MT, HVA and noradrenaline bitartrate were obtained from Sigma (St Louis, MO, USA). [^{3}H]-5-HT creatinine sulfate (30.0 Ci/mmol) and [^{14}C]-β-PEA hydrochloride (41.8 Ci/mmol) were obtained from NEN Chemicals (Boston, MA, USA). Insulin was obtained from Novo Nordisk (Actrapid Novo Nordisk, Bargsvaerd, Denmark).

Statistics: Results are mean ± SE of values for the indicated number of determinations. Maximal velocity (V_{max}) and Michäelis–Menten coefficient (K_m) values were calculated from non-linear regression analysis using GraphPad Prism statistics software package (GraphPad Software Inc., La Jolla, CA, USA). Statistical analysis was performed as follows: Student's *t*-test for unpaired comparisons and two-way repeated measures analysis of variance, followed by Student–Newman–Keuls test for significant differences for paired comparisons. A $P < 0.05$ was assumed to denote a significant difference.

Results

The daily sodium intake was similar between the obese and control groups (0.18 ± 0.05 versus 0.19 ± 0.05 mmol/day) throughout the study. After twelve weeks of exposure to

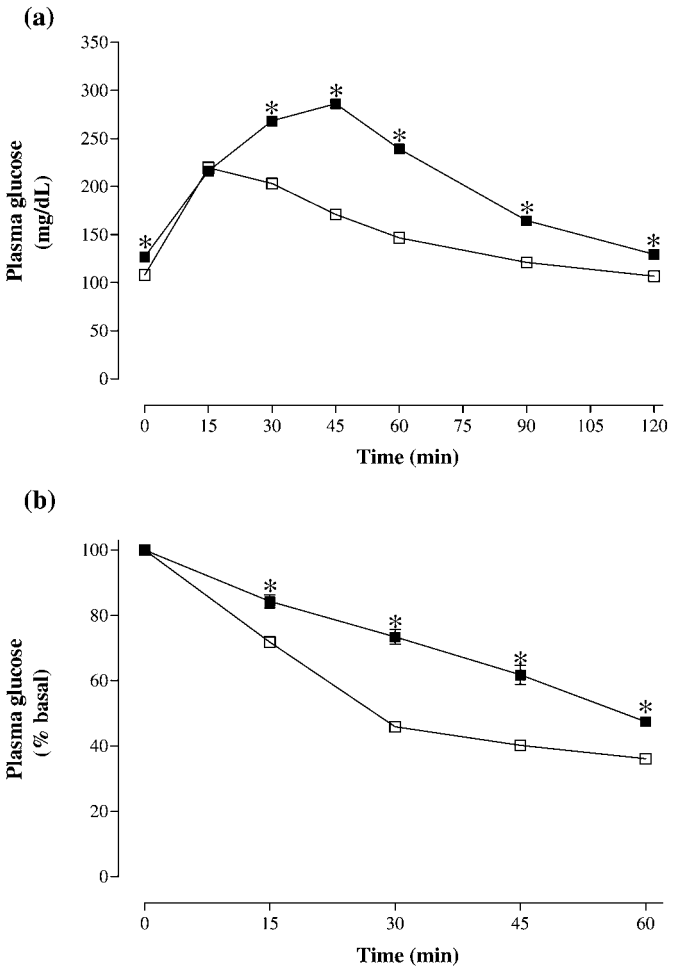

Figure 1 (a) Glucose tolerance test and (b) insulin resistance test in control (□) and obese (■) mice. Symbols represent means of 6–8 experiments per group, and error bars represent SE. *Significantly different from values in control mice ($P < 0.05$)

Table 2 Urinary levels of dopamine, L-Dopa, DOPAC, 3-MT, HVA and noradrenaline under normal sodium intake (NS) or high sodium intake (HS, mean values of days 1 and 2) in control and obese mice

	NS		HS	
	Control	Obese	Control	Obese
Dopamine (nmol/day)	3.7 ± 0.7	0.6 ± 0.1*	8.6 ± 1.4†	0.5 ± 0.1*
L-Dopa (nmol/day)	1.9 ± 0.2	1.3 ± 0.3	3.0 ± 0.4†	1.4 ± 0.2
DOPAC (nmol/day)	6.7 ± 0.7	3.7 ± 0.9*	8.1 ± 1.1	3.2 ± 0.7*
3-MT (nmol/day)	42.4 ± 5.1	1.9 ± 0.4*	45.4 ± 3.8	2.0 ± 0.4*
HVA (nmol/day)	90.6 ± 14.3	5.6 ± 0.9*	74.6 ± 10.5	7.8 ± 1.8*
Noradrenaline (nmol/day)	1.7 ± 0.3	4.0 ± 1.1*	2.0 ± 0.2	4.6 ± 1.0*

L-Dopa, L-3,4-dihydroxyphenylalanine; DOPAC, 3,4-dihydroxyphenylacetic acid; 3-MT, 3-methoxytyramine; HVA, homovanilic acid
Values are mean ± SE; $n = 6$ to 8 experiments per group
*Significantly different from values in control mice ($P < 0.05$)
†Significantly different from values in normal sodium (NS) intake mice ($P < 0.05$)

the HFHSC diet, obese mice presented significantly increased body weight and body fat, as well as plasma glucose, cholesterol and triglycerides when compared with control mice (Table 1). Furthermore, obese mice presented glucose intolerance (Figure 1a) and insulin resistance (Figure 1b). Under HS intake, control and obese mice ingested the same amount of sodium on the first (2.1 ± 0.2 versus 2.0 ± 0.3 mmol/day), second (1.8 ± 0.2 versus 1.7 ± 0.3 mmol/day) and third (2.4 ± 0.3 versus 1.8 ± 0.3 mmol/day) days. No significant differences were observed in kidney weight, creatinine clearance and fractional excretion of sodium between obese and corresponding control groups (Table 1). Obese mice presented a higher heart rate as well as increased systolic and diastolic blood pressures in comparison to control mice (Table 1).

Daily urinary excretion of dopamine, DOPAC, 3-MT and HVA excretion were significantly lower in obese than in corresponding control groups (Table 2). However, daily urinary excretion of dopamine precursor, L-DOPA, was similar between obese and control mice (Table 2). In control mice, the HS diet induced an increase in absolute urinary dopamine and L-DOPA excretion (Table 2), but not in obese mice. Renal cortex tissue and plasma levels of L-Dopa and dopamine did not differ between obese and corresponding control groups (Table 3). Urinary and plasma noradrenaline levels were significantly higher in obese mice than in control mice whereas renal cortex tissue noradrenaline levels did not differ between obese and control mice (Tables 2 and 3).

Table 3 Plasma and renal cortex levels of dopamine and L-Dopa and noradrenaline during normal sodium intake (NS) in control and obese mice

	Control	Obese
Plasma levels		
Dopamine (pmol/mL)	31.5 ± 4.8	32.2 ± 3.2
L-Dopa (pmol/mL)	13.2 ± 2.6	15.9 ± 1.7
Noradrenaline (pmol/mL)	16.6 ± 3.1	44.0 ± 6.9*
Renal cortex levels		
Dopamine (pmol/g)	106.1 ± 14.0	114.4 ± 8.9
L-Dopa (pmol/g)	563.8 ± 60.4	647.4 ± 42.7
Noradrenaline (pmol/g)	4170.2 ± 278.2	4388.4 ± 412.2

L-Dopa, L-3,4-dihydroxyphenylalanine
Values are mean ± SE; $n = 6$ to 8 experiments per group
*Significantly different from values in control mice ($P < 0.05$)

The AADC activity was determined in homogenates of renal cortex with L-Dopa as substrate, which resulted in a concentration-dependent formation of dopamine

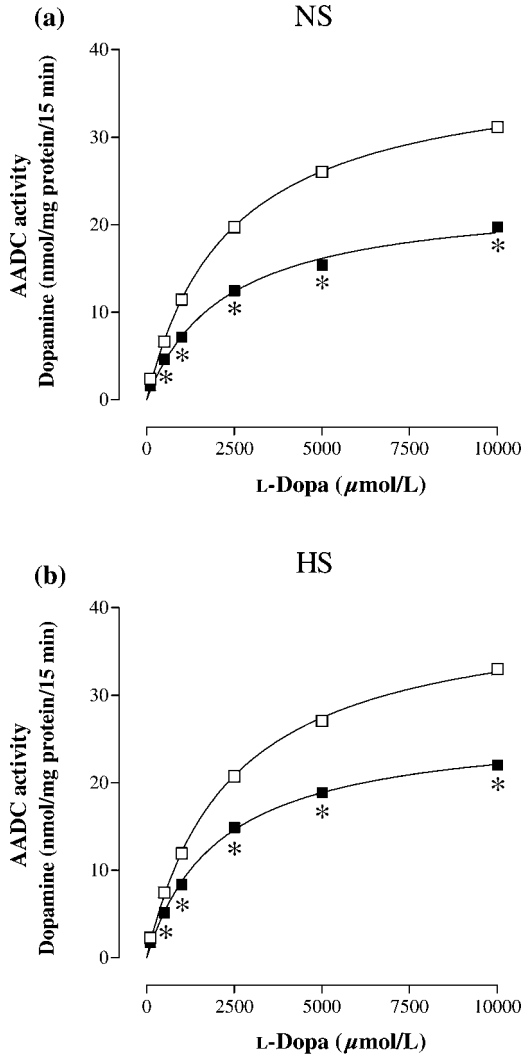

Figure 2 Renal aromatic L-amino acid decarboxylase (AADC) activity (a) under normal sodium intake (NS) or (b) high sodium intake (HS) in control (□) and obese (■) mice. AADC activity is expressed as the rate of formation of dopamine versus concentration of L-Dopa. Symbols represent means of 6–8 experiments per group and error bars represent SE. *Significantly different from values in control mice ($P < 0.05$)

Table 4 Kinetic parameters (V_{max} and K_m) of aromatic L-amino acid decarboxylase (AADC) under normal sodium intake (NS) or high sodium intake (HS) in homogenates of renal cortex obtained from control and obese mice

	NS		HS	
	Control	Obese	Control	Obese
V_{max} (nmol/mg protein/15 min)	38.3 ± 0.2	23.3 ± 0.3*	40.3 ± 0.2†	26.7 ± 0.1*,†
K_m (mmol/L)	2.3 ± 0.4	2.2 ± 0.8	2.3 ± 0.3	2.2 ± 0.6

Values are mean ± SE; $n = 6$ to 8 experiments per group
*Significantly different from values in control mice ($P < 0.05$)
†Significantly different from values in normal sodium (NS) intake mice ($P < 0.05$)

Table 5 Kinetic parameters (V_{max} and K_m) of catechol-*O*-methyltransferase (COMT) and monoamine-oxidase (MAO-A and MAO-B) in homogenates of renal cortex obtained from control and obese mice

	COMT		MAO-A		MAO-B	
	Control	Obese	Control	Obese	Control	Obese
V_{max} (nmol/mg protein/15 min)	2.0 ± 0.1	2.1 ± 0.1	7.2 ± 0.1	5.1 ± 0.1*	2.0 ± 0.1	2.2 ± 0.1
K_m (μmol/L)	25.7 ± 2.9	25.2 ± 2.6	101.4 ± 15.1	74.1 ± 5.5	0.3 ± 0.1	0.3 ± 0.1

Values are mean ± SE; $n = 6$ to 8 experiments per group
*Significantly different from values in control mice ($P < 0.05$)

(Figure 2). The decarboxylation reaction was a saturable process, with K_m values of the same magnitude in both groups of mice (Table 4). Under NS and HS intake, the V_{max} for renal AADC activity was significantly lower in obese than in control mice (Table 4 and Figure 2). Both in control and obese mice, the HS diet induced an increase in renal AADC activity (Table 4 and Figure 2). The MAO-A, MAO-B and COMT activities were determined during the NS diet in homogenates of renal cortex and the kinetic parameters are shown in Table 5. The enzymatic reactions were a saturable process, with K_m values of the same magnitude in both groups of mice. The V_{max} for renal MAO-A activity was significantly lower in obese than in control mice. No significant differences were observed in MAO-B or COMT activities among groups.

When one looks to daily urinary sodium excretion during the NS or HS diet (Figure 3), the control and obese mice are able to excrete the same amount of sodium in the last two days of the HS diet. During the first day of the HS diet, the increase of sodium excretion observed in obese mice was 34 ± 8% lower than the increase of sodium excretion observed in control mice (Figure 3).

Discussion

The exposure of C57BL6J mice to the HFHSC diet was accompanied by obesity, insulin resistance, hyperinsulinemia, hyperglycemia, glucose intolerance and hypertension, as already described.[26–28] This model was considered one of the most reliable and clinically relevant experimental models in obesity and was proven to be useful for mechanistic studies and as a tool for developing novel therapeutic interventions.[33] To our knowledge, there is no information on dopaminergic system activity in this diet-induced obesity model. The study is focused on sodium handling, blood pressure, sympathetic activity and the renal dopaminergic system in this mouse model of diet-induced obesity. Our results show an increased sympathetic activity associated with a defective renal dopaminergic system, suggesting that this may favour sodium retention and raise blood pressure.

Our results demonstrate that the renal dopaminergic system of obese mice has a deficient ability to produce dopamine, during both NS and HS intake, as evidenced by decreased urinary dopamine and dopamine metabolite excretion. The explanation for the decreased urine dopamine excretion in obese mice is related with the marked decrease observed in AADC activity in renal proximal tubules from these mice. In addition, kidneys from obese mice show a reduced ability in deaminating dopamine, as evidenced by decreased urinary DOPAC and HVA excretion, as well as decreased renal MAO-A activity. The reduced renal dopamine deamination activity may

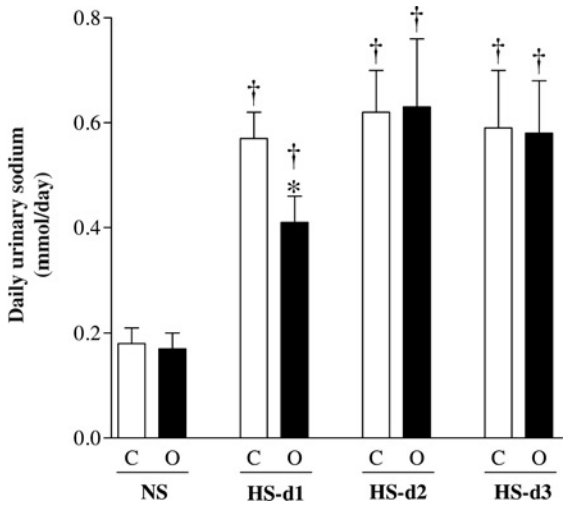

Figure 3 Daily urinary levels of sodium under normal sodium intake (NS, day 0) or high sodium intake (HS) on days 1 (HS-d1), 2 (HS-d2) and 3 (HS-d3), in control (C) and obese (O) mice. Bars or symbols represent means of 6–8 experiments per group and error bars represent SE. *Significantly different from values in control mice (C) ($P < 0.05$). †Significantly different from values in normal sodium (NS) intake mice ($P < 0.05$)

constitute a compensatory response to the renal decreased dopamine availability.

In rats, HS intake has been shown to stimulate the renal dopaminergic system, as evidenced by increases in the urinary excretion of dopamine and renal AADC activity.[34–37] Accordingly, following HS intake, absolute urinary dopamine excretion increased in control mice; however, this did not occur in obese mice. Since AADC activity increased in HS intake when compared with NS intake in both control and obese mice, this suggests that the failure to increase urinary dopamine excretion in obese mice, during HS intake, may be also due to decreased L-Dopa uptake in renal proximal tubule cells. This suggestion is in agreement with the proposal that the rate-limiting step in dopamine synthesis is the uptake of L-Dopa,[38] which was demonstrated to be mediated through amino acid transporters.[39–42]

In agreement with our findings, there are reports of monogenic models of obesity (leptin receptor gene mutation) already suggesting defective dopaminergic systems, which may be responsible for diminished natriuretic responses.[19–20] On the other hand, hyperinsulinemia was suggested to induce a defect in renal dopamine D_1 receptor signaling in opossum kidney cells, which may contribute to sodium retention and hypertension.[43] Also, insulin resistance was suggested to be responsible for impaired renal dopamine D_1-like receptor signaling and function, as treatment with the insulin sensitizer, rosiglitazone, normalized these parameters in Zucker fatty rats.[44]

Furthermore, insulin resistance and compensatory hyperinsulinemia was related with the development of salt sensitivity in essential hypertension.[45,46] Our HFHSC diet-induced obesity mouse model presented insulin resistance, hyperinsulinemia and hyperglycemia, which may all contribute to a defective renal dopaminergic system and consequently for the hypertensive state.

Sympathetic hyperactivity has been associated with obesity[20] and the metabolic syndrome.[21–22] In addition, insulin infusions in human subjects have been shown to enhance the sympathetic nervous system.[47,48] The observation that adrenergic stimulation of renal adrenergic nerves or infusion of low doses of noradrenaline, an adrenergic agonist, produce an increase in renal tubular sodium reabsorption,[49,50] suggests that the adrenergic system is capable of regulating renal tubular sodium transport. In fact, noradrenaline was suggested to promote renal sodium reabsorption in proximal convoluted tubules by increasing Na^+/K^+-ATPase activity.[12] Also, overactivation of the sympathetic system by noradrenaline induced increases in the expression of sodium transporters (NHE-3, NBC-1 and BSC-1), suggesting that this may contribute to sodium retention in pathological conditions associated with increased sympathetic activity.[13] Since obese mice presented increased urinary and plasmatic noradrenaline levels, associated with a higher heart rate when compared with control mice, this suggests an increased sympathetic activity, which may contribute to the observed hypertension.

In obese mice, a blunted increase in urinary excretion of sodium during the first day of HS intake was observed, suggesting an initial state of sodium retention in these animals. This could account for the observed deficient renal dopaminergic system and increased sympathetic activity. However, in the last two days of the HS diet, daily urinary sodium excretion was identical in control and obese mice, suggesting that other natriuretic systems may be involved in sodium homeostasis control. Indeed, sodium and fluid reabsorption by the proximal tubule is controlled by many hormones and neurotransmitters including dopamine, norepinephrine, angiotensin II, insulin, atrial natriuretic peptide, endothelins, glucocorticoids and others.[1]

In conclusion, in our mouse model of diet-induced obesity, hyperinsulinemia, insulin resistance and increased sympathetic tone are associated with blunted renal dopaminergic activity. It is suggested that this may contribute to impaired sodium excretion and increased blood pressure in obesity.

Author contributions: All authors participated in the interpretation and analysis of the data as well as in the review of the manuscript.

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