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EFFECTS OF HIGH FAT DIET ON THE BASAL ACTIVITY OF THE HYPOTHALAMUS-PITUITARY-ADRENAL AXIS IN MICE: A SYSTEMATIC REVIEW

Hanna E. Auvinen
Johannes A. Romijn
Nienke R. Biermasz
Louis M. Havekes
Johannes W. A. Smit
Patrick C.N. Rensen
Alberto M. Pereira

Hormone and Metabolic Research 2011; 43: 899-906

ABSTRACT

Background: Hypothalamus-pituitary-adrenal-axis activity is suggested to be involved in the pathophysiology of the Metabolic syndrome. In diet-induced obesity mouse models, features of the Metabolic syndrome are induced by feeding high fat diet. However, the models reveal conflicting results with respect to the hypothalamus-pituitary-adrenal-axis activation.

Aim: To assess the effects of high fat feeding on the activity of the hypothalamus-pituitary-adrenal-axis in mice.

Methods: PubMed, EMBASE, Web of Science, the Cochrane database, and Science Direct were electronically searched and reviewed by 2 individual researchers

Study selection: We included only original mouse studies reporting parameters of the hypothalamus-pituitary-adrenal-axis after high fat feeding, and at least one basal corticosterone level with a proper control group. Studies with adrenalectomized mice, transgenic animals only, high fat diet for less than two weeks, or other interventions besides high fat diet, were excluded.

Results: Twenty studies were included. The hypothalamus-pituitary-adrenal-axis evalution was the primary research question in only 5 studies. Plasma corticosterone levels were unchanged in 40%, elevated in 30%, and decreased in 20% of the studies. The effects in the peripheral tissues and the central nervous system were also inconsistent. However, major differences were found between mouse strains, experimental conditions, and the content and duration of the diets.

Conclusion: This systematic review demonstrates that the effects of high fat feeding on the basal activity of the Hypothalamus-pituitary-adrenal-axis in mice are limited and inconclusive. Differences in experimental conditions hamper comparisons and accentuate the need for standardized evaluations to discern the effects of diet-induced obesity on the hypothalamus-pituitary-adrenal-axis.

INTRODUCTION

The metabolic syndrome (MetS) is a cluster of metabolic abnormalities that identifies individuals at high risk for cardiovascular disease (1, 2). These metabolic abnormalities include abdominal obesity, hypertension, dyslipidemia, and insulin resistance. The concept of the MetS is a subject of debate, because the pathophysiological basis of this syndrome is unclear (3). In addition, the combination of cardiovascular risk factors does not add to the risk related to the individual risk factors for cardiovascular disease (4). Nonetheless, these individual, well-recognized cardiovascular risk factors have all been associated with increased cardiovascular morbidity and mortality in the general population (1, 2, 4).

Several lines of evidence suggest that alterations in the activity of the hypothalamus-pituitary-adrenal (HPA)-axis may be involved in the development of the MetS. Glucocorticoids (GC) (cortisol in humans and corticosterone in rodents) are secreted by the adrenals in response to a stressor, in order to induce the required behavioral and metabolic adaptations to be able to adequately cope with the stressor (fight or flight). The metabolic effects of GC include both peripheral and central effects. Whereas the peripheral effects are directed towards recruitment of energy availability by reduction of energy stores for gluconeogenesis, the central effects of glucocorticoids are anabolic and directed towards augmentation of energy stores by adjusting feeding behavior and intake of palatable foods to compensate for the energy loss. As a consequence, increased cortisol exposure, like during chronic stress, will further increase insulin levels and food intake, facilitating the development of obesity and the MetS (5, 6).

This is first exemplified by patients with Cushing's syndrome (CS), a rare disorder caused by prolonged excessive exposure to glucocorticoids. Patients with CS have a phenotypical resemblance to and fulfill the criteria for, the MetS (7). These patients have a markedly increased cardiovascular morbidity and mortality (8), suggesting that excessive exposure to glucocorticoids is involved in the pathogenesis of MetS and central obesity. Second, patients with MetS show increased activity of the HPA-axis (9), but the underlying mechanisms are only partially understood (10). Third, manipulation of cortisol exposure at the tissue level through stimulation, or abrogation, of 11β-hydroxysteroid dehydrogenase type-1 (11-β-HSD-1) activity can increase, or regress, the fat accumulation in visceral depots, and well as other features of the MetS (11, 12).

In animal models of diet-induced obesity (DIO), common features of the MetS, like insulin resistance and obesity are easily induced by feeding of high fat diet (HFD). However, these experimental mouse models of obesity and the MetS reveal conflicting results with respect to whether the HPA-axis is activated. These discrepancies might be explained by methodological differences between the studies, including differences in rodent models. Therefore, the aim of the present systematic review was to critically compare the data available in mice on the effects of HFD feeding on basal, non-stressed activity of the HPA-axis, and to discuss possible explanations for the observed differences.

METHODS

Search strategy

We performed a systematic search in PubMed, EMBASE, Web of Science, the Cochrane database, and Science Direct, for published studies on the association between HFD feeding and activity of the HPA-axis. The following search strategy was used: for PubMed: *(high fat diet OR high*

lipid diet OR high fat diets OR high lipid diets OR western-type diet OR western-type diets OR "high-fat" OR Dietary Fats OR (diet-induced obesity)) AND (HPA-axis[tw] OR (("Hypothalamo-Hypophyseal System"[mesh] OR "Pituitary-Adrenal System"[mesh] OR hpa[tw]) AND axis[tw]) OR Hypothalamo-Pituitary-Adrenal[tw] OR Hypothalamus-pituitary-adrenal[tw] OR glucocorticoid OR glucocorticoids OR corticosterone) AND (mice OR mouse); for EMBASE: *((high fat diet OR high lipid diet OR high fat diets OR high lipid diets OR western-type diet OR western-type diets OR "high-fat" OR Dietary Fats OR diet-induced obesity).mp OR exp fat intake/ OR exp lipid diet/) AND (hypothalamus hypophysis adrenal system/ OR exp glucocorticoid/ OR corticosterone/ OR (HPA-axis OR ((Hypothalamo-Hypophyseal OR Pituitary-Adrenal OR hpa) AND axis) OR Hypothalamo-Pituitary-Adrenal OR Hypothalamus-pituitary-adrenal OR glucocorticoid* OR corticosterone).mp) AND (exp mouse/ OR mice.af OR mouse.af)*; for Web of Science: *TS=((high fat diet OR high lipid diet OR high fat diets OR high lipid diets OR western-type diet OR western-type diets OR "high-fat" OR Dietary Fats OR (diet-induced obesity)) AND (HPA-axis OR ((Hypothalamo-Hypophyseal OR Pituitary-Adrenal OR hpa) AND axis) OR Hypothalamo-Pituitary-Adrenal OR Hypothalamus-pituitary-adrenal OR glucocorticoid OR glucocorticoids OR corticosterone) AND (mice OR mouse))*; for Cochrane: *(high fat diet OR high lipid diet OR high fat diets OR high lipid diets OR western-type diet OR western-type diets OR "high-fat" OR Dietary Fats OR (diet-induced obesity)) AND (HPA-axis OR ((Hypothalamo-Hypophyseal OR Pituitary-Adrenal OR hpa) AND axis) OR Hypothalamo-Pituitary-Adrenal OR Hypothalamus-pituitary-adrenal OR glucocorticoid OR glucocorticoids OR corticosterone) AND (mice OR mouse);* for ScienceDirect: *TITLE((high fat diet OR high lipid diet OR high fat diets OR high lipid diets OR western-type diet OR western-type diets OR "high-fat" OR Dietary Fats OR (diet-induced obesity)) AND (HPA-axis OR ((Hypothalamo-Hypophyseal OR Pituitary-Adrenal OR hpa) AND axis) OR Hypothalamo-Pituitary-Adrenal OR Hypothalamus-pituitary-adrenal OR glucocorticoid OR glucocorticoids OR corticosterone) AND (mice OR mouse))*; for Academic Search Premier: *((high fat diet OR high lipid diet OR high fat diets OR high lipid diets OR western-type diet OR western-type diets OR "high-fat" OR Dietary Fats OR (diet-induced obesity)) AND (HPA-axis OR ((Hypothalamo-Hypophyseal OR Pituitary-Adrenal OR hpa) AND axis) OR Hypothalamo-Pituitary-Adrenal OR Hypothalamus-pituitary-adrenal OR glucocorticoid OR glucocorticoids OR corticosterone) AND (mice OR mouse))*.

In addition, the references of relevant articles were checked for additional articles. The search was performed on January 27, 2011. Only original articles were included. We used the following exclusion criteria: adrenalectomized animals, transgenic animals only, duration of HFD of less than two weeks, and other interventions disabeling the interpretation of the effect of the HFD per se. In addition, studies were only included if 1) the effects of HFD were compared with a control group on standard chow or low fat diet (LFD), and 2) at least one basal (thus non-stressed) corticosterone sample was available for both groups.

Data review

The following data were extracted from each study: mouse strain, age and/or bodyweight at baseline, body weight gain, housing conditions, dietary intervention (duration and content of the diet (percentage of calories provided as fat)), and specific parameters of HPA-axis activity: circulating corticosterone concentrations, 11-β-HSD-1 activity, corticotrophin-releasing hormone (CRH) adrenocorticotropic hormone (ACTH), and glucocorticoid receptor (GR) expression in peripheral tissues and/or the central nervous system (when evaluated). In addition, we evaluated the clock

hour of evaluation (related to the circadian nadir or not), whether single or multiple time points were used for sampling of blood, and whether circulating corticosterone was measured only or combined with other central and/or peripheral parameters of HPA-axis activity.

RESULTS

The search strategy identified a total of 218 articles: PubMed: n=142; EMBASE: n=139, of which 26 were unique; Web of Science: n=132, of which 39 were unique; none in the COCHRANE database, ScienceDirect: n=6, all unique, and 34 in Academic Search Premier, of which 5 were unique. Of these, 150 papers were excluded on the basis of title and abstract. The remaining 68 studies were retrieved for full evaluation, of which 20 studies fulfilled the in- and exclusion criteria. In only 5 of these 20 selected studies, evaluation of selective parameters of the HPA-axis was the primary research question. Details of these 20 studies are summarized in Table 1.

Mouse characteristics, housing, and diets

The most commonly used mice were male C57Bl/6 mice. 8 studies (13-15, 23, 24, 28-30) evaluated the effects of HFD in C57Bl/6 mice only, and one study only in A/J mice (18). Another 6 studies compared C57Bl/6 mice either with A/J (19), or with transgenic mice: Leptin deficient C57Bl/6J Lep ob/ob (17), diabetic KKAy and ob/ob (21), 11-β-HSD-1-knockout (KO) (16, 22), and glucocorticoid receptor haploinsufficient GRβgeo/+ (27) mice. The remaining 5 studies used polygenic fat and lean mice from inbred lines (20), Balb/c mice (25), male NIH Swiss mice (26), or compared glucocorticoid receptor activity regulating FK506-binding protein 52 heterozygote (FKBP52+/-) male mice or kappa-opioid receptor knockout (KOR-KO) mice with their wild type littermates (31, 32).

At baseline, the mean age of the mice varied from 3-19 weeks, and in one study from 6-9 months (20). In accordance with these variations in age, body weight at baseline (when documented) varied from < 10 g to 30 g.

Housing conditions were not specified in 8/20 studies. In the remaining 12 studies, mice were pair-housed in 3 studies, 3-4 per cage in one study, and single housed (for the entire study period or for the last week before sampling) in 8 studies.

Acclimation period was applied in nine studies. In 2 studies (20, 27) time was not specified. Another 6 studies (14, 15, 18, 21, 23, 25) had an acclimation period of one week (handling mentioned in only a few). Finally, one study (29) reported a 4-week acclimation period at the end of the experiment.

The duration of the diets varied between 2 and 30 weeks, and the relative contribution of calories derived from fat between 32% and 60% (within the HFD) and between 6.5% and 16% (within the LFD).

The effects of HFD on circulating corticosterone concentrations (n=20 studies)

The evaluation of circulating corticosterone levels was limited to a single sample in 85% (17/20) of the studies. Blood samples were obtained between 8-11 am in 12 studies, whereas the time of sampling was not specified in 6 other studies. Three studies assessed diurnal variation of corticosterone levels, by using 2 samples (8-10 am and 7 pm) (27), or by using samples obtained every 4 h (24), or even every 2 h (29).

HFD did not affect circulating corticosterone levels in 8 studies (13, 14, 18, 19, 21, 23, 25, 32) (all obtained a single blood sample only). 3 of these 8 studies actually reported corticosterone

Table 1. Studies in mice on the effects of High Fat Diet feeding on basal, non-stressed activity of the HPA axis.

	Author (ref)	Mouse strain	Mean age / weight at baseline	Housing	Diet (HFD / LFD % cal as fat)	Duration of diet	Weight gain
1	Herberg L *et al*. 1975 (13)	C57Bl/6	-	(NS	-	4 wks	-
2	Ziotopoulou M *et al*. 2000 (14)	C57Bl/6J	4wks / 20.6 g	NS	43% / 6.5%	2 wks	3.3 *vs* 2.3 g
3	Moraes RC *et al*. 2003 (15)	C57Bl/6J	4 wks	pair	36% / 3%	8 wks	11 *vs* 6 g
4	Morton NM *et al*. 2004b (16)	MF1 WT 11 β -HSD-KO C57Bl/6J-11β--HSD-KO	'adult' / 25-30 g	Standard single last week	58 / 11%	18 wks	15 *vs* 5 g
5	Morton NM *et al*. 2004a (17)	C57Bl/6J A/J C57Bl/6-JLep obob	'adult'	Standard; single last week	58% / 11%	2 wks 18 wks	-
6	Bullen JW Jr *et al*. 2004 (18)	A/J	4-9 wks	NS	45% / 10%	4 wks	4 to 5 g
7	Michel C *et al*. 2005 (19)	C57Bl/6J AJ	23-28 g	pair	65% / 63% cal as fat or starch	25 days	5 g (BL6)/ 1 g (A/J)
8	Morton NM *et al*. 2005 (20)	polygenic fat and lean mice from inbread lines	6-9 months	Single	58% / 11%	18 wks (after selection: fat vs lean mice)	2.5 fold higher in fat mice on HFD
9	Alberts P *et al*. 2005 (21)	KKAy ob/ob C57Bl/6J	11-15 wks 16 wks 19 wks	single	HFD: 32.5 kcal% fat with 0.01% chol LFD:10 kcal% fat	4 wks	Body weight 44.9 vs 44.4g 50.4 vs 48.7 LFD: 28.5 g (no HFD)

Table legends: WT: wild type; HFD: high Fat Diet; LFD: low Fat diet; Chol: cholesterol; NS: not specified; Cort: corticosterone; PVN: paraventricular nucleus of the hypothalamus; 11-β-HSD-1: 11 beta hydroxysteroid dehydrogenase type 1; CRH: corticotrophin-releasing hormone ACTH: adrenocorticotropic hormone; GR: glucocorticoid receptor; 11–DHC:11-dehydrocorticosterone; AT: adipose tissue

Evaluation time points	Mean Plasma corticosterone (HFD / LFD)	Adrenal / thymic weight (HFD / LFD)	Peripheral Cort activity	Central Nervous System
-	2 µg/dl No effect of diet	-	-	-
8-9.30 a.m (One sample)	No effect of diet (data not shown)	-	-	-
Not specified (NS) (one sample)	47 / 29 ng/ml	-	Various genes (not glucose related)	-
8 a.m. (one sample)	18 / 31 nmol/l 58 / 57 nmol/l No effect of the diet	-	↓intra-AT (visceral + epididymal) cort levels in C57BL/6J–11-β –HSD-1-KO *vs* wildtype C57BL/6J on LFD: (159 ng/g; 477; and HFD: (404 *vs* 562 ng/g)	-
8 a.m. (one sample)	BL6: 170 / 100 nmol/l A/J: 100 / 60 nmol/l	-	↓ AT 11-β-HSD-1 after HFD (more in BL6)	-
2-3 h after lights on (one sample, under CO^2 narcosis)	Not different at 1,2,3,4 wks (data not shown)	-	-	PVN: CRH-R: no difference
NS (one sample after anaesthesia)	BL6: 80 / 62 mmol/l A/J: 92 / 88 nmol/l No effect of the diet	-	-	PVN: CRH: no effect of diet Amygdala: CRH↑ in BL6; no effect of diet
8 a.m. (one sample)	39 / 86 nmol/l (fat *vs* lean mice: effect of breeding)	↓ adrenal and ↑ thymus in fat mice Diet: NS	↓ AT + ↑ liver 11-β-HSD-1	GR in PVN and Hippocampus: not different
9-11 a.m. (one sample)	0.23 / 0.17 µM 0.92 / 1.30 µM BL6: (LFD): 0.08 µM No effect of the diet	-	-Liver cort 3.0 -5.1 and 6.2- 8.1–fold, and 11–DHC 3.4-3.6 and 6.7-8.2–fold ↑ in KKAy and ob/ob *vs* WT) - Mesenteric AT cort 2.7-4.2–fold ↑, and 11-DHC 2-4–fold ↑ in ob/ob *vs* in KKAy mice No C57/BL6 (nM/Kg) - Epididymal AT cort 3.0- 6.2–fold ↑,and 11DHC 1.8- 2.0–fold ↑ in ob/ob *vs* KKAy mice, WT not shown	-

Table 1. Studies in mice on the effects of High Fat Diet feeding on basal, non-stressed activity of the HPA axis. Cd.

	Author (ref)	Mouse strain	Mean age / weight at baseline	Housing	Diet (HFD / LFD % cal as fat)	Duration of diet	Weight gain
10	Densmore VS *et al*. 2006 (22)	C57Bl/6J 11-B-HSD-KO	6 wks / 25-30 g	pair	58% / 11%	2 or 18 wks	15 *vs* 5 g
11	Luque RM *et al*. 2006 (23)	C57Bl/6J	4 wks	single	60% / 10%	16 wks	25 *vs* 15 g
12	Kohsaka A *et al*. 2007 (24)	C57Bl/6J	6 wks	NS	45% / 16%	6 wks	8 vs 4 g
13	Chen H *et al*. 2007 (25)	Balb/c	5 wks	NS	32% / 12%	7 wks	8 *vs* 5 g
14	McClean PL *et al*. 2007 (26)	NIH Swiss	8 wks	single	45% / 10%	160 days	Final mean body weight 55 *vs* 38 g
15	MichailidouZ *et al*. 2008 (27)	C57Bl/6J GRβgeo/+	≤ 10 g	Standard; single for sampling	58% / 11%	22 wks	40 *vs* 20 g
16	Liu Y *et al*. 2008 (28)	C57Bl/6	6 wks	NS	58% / 11%	30 wks	Final mean body weight 56 *vs* 32 g
17	Veniant MM *et al*. 2009 (29)	C57Bl/6	3 wks (HFD) 16 wks (chow)	Single for 4 last weeks	60% / chow	13 wks	-
18	Matsumoto S *et al*. 2009 (30)	C57Bl/6J	4 wks	NS	2% chol vs normal diet	2 wks	7 *vs* 7 g
19	Warrier M *et al*. 2010 (31)	FKBP52+/- WT	2 months	NS	45% / 12%	4 wks	22% *vs* 7% 22% *vs* 7%
20	Czyzyk TA *et al*. 2010 (32)	129S6 WT KOR-KO	7-8 wks	3-4 per cage	45% / 5%	16 wks	15 *vs* 4.6 g

Table legends: WT: wild type; HFD: high Fat Diet; LFD: low Fat diet; Chol: cholesterol; NS: not specified; Cort: corticosterone; PVN: paraventricular nucleus of the hypothalamus; 11-β-HSD-1: 11 beta hydroxysteroid dehydrogenase type 1; CRH: corticotrophin-releasing hormone ACTH: adrenocorticotropic hormone; GR: glucocorticoid receptor; 11–DHC:11-dehydrocorticosterone; AT: adipose tissue

Evaluation time points	Mean Plasma corticosterone (HFD / LFD)	Adrenal / thymic weight (HFD / LFD)	Peripheral Cort activity	Central Nervous System
Between 8-10 (one sample)	2 wk: 40 / 130 nmol/l 18 wk: 170 (HFD) nmol/l	-	-	-PVN: 2 wks: ↑11 b-HSD in arcuate nucl 18 wk: reversed - Hippocampus: no change in 11-β-HSD-1: (2 nor 18 wks)
Between 8-11 (one sample)	0.9 / 0.7 ng/ml No effect of the diet	-	-	-
Every 4 h	2-15 / 3-20 µg/dl	-	-	-
NS (one sample after anaesthia)	198 / 221 ng/ml No effect of the diet	-	-	-
NS (one sample)	Approx 55 / 20 ng/ml (229%↑ in HFD)	-	-	-
Diurnal 8-10 h, 19 h	50-100 (m-e) / 25-75 (m-e) nmol/l	7 *vs* 5 gr (P<0.05)	Genotype ↓↑ Diet: not shown	PVN: genotype ↓↑ Diet: POMC not different Hippocampus: Genotype ↓↑ Diet not shown
9-10 am (one sample)	36 / 23 ng/ml	-	-	-
Diurnal Every 2 h from 4.30-20.30 h	26 / 42 (nadir) 526 / 526 ng/ml (peak)	-	Influence of time on effectiveness of 11-β-HSD-1 Inhibition	-
8 a.m. (one sample)	Appox 50 / 30 ng/ml	-	-	POMC mRNA ↑ after high Chol diet (circ ACTH also ↑)
NS Sample via retro-orbital sinuses (requires sedation)	260 / 180 ng/ml 190 / 225 ng/ml No effect of the diet for WT	-	-	-
11 a.m.	76 / 114 ng/ml	-	-	-

concentrations in conscious conditions, which varied widely (more than 200 fold): from 0.7-0.9 ng/ml (23), 27.7 ng/ml (21), to 76 ng/ml (32) in the morning nadir. 3 out of the 8 studies reported corticosterone concentrations under anesthesia (18, 19, 25) and even in the millimolar range (19). 2 remaining studies did not specify the time of the sampling (13) or did not report the corticosterone concentrations (14).

HFD increased corticosterone concentrations in 6 other studies (15, 17, 26, 27, 28, 30) after 2, 8, 18, 23, and 30 weeks of diet. In C57Bl/6 mice the corticosterone concentrations varied from 47 vs 29 ng/ml, 59 vs 35 ng/ml, 36 vs 23 ng/ml, to 50 vs 30 ng/ml (15, 17, 28, 30) and 35 *vs* 21 ng/ml (in A/J mice) (17). 3 of these studies did not specify the time of sampling (15, 26, 28) and one did not specify the strain (30).

HFD decreased corticosterone concentrations in 4 other studies (22, 24, 29, 31), 2 of which sampled corticosterone more than once daily. The first study sampled plasma corticosterone levels every 4 h and found that HFD decreased both nadir (20 *vs* 30 ng/ml) and peak (150 *vs* 200 ng/ml) corticosterone concentrations after 6 weeks of the diet (24). In contrast, Véniant *et al*. (29) found that HFD decreased the nadir (26 *vs* 42 ng/ml) corticosterone concentrations evaluated every 2 h whereas HFD did not affect peak corticosterone (526 ng/ml) after 13 weeks of the diet. Finally, one study documented that HFD decreased corticosterone levels at 2 weeks but increased corticosterone concentrations after 18 weeks of the diet (22). The remaining study showed a decrease in the morning nadir, but the sample was obtained under anesthesia.

The remaining one study reported an effect of genotype or breeding on circulating corticosterone concentrations after HFD: MF1-11-β-HSD-1-KO and C57Bl/6J-11-β-HSD-1-KO mice had higher circulating corticosterone concentrations than their wild type littermates (16). In addition, other studies reported the effect of genotype or breeding on cortcosterone concentrations: C57Bl/6J showed higher corticosterone concentrations than A/J mice (17) and polygenic lean mice from inbred lines had higher corticosterone concentrations after 18 weeks of HFD than their fat littermates (86 *vs* 39 nmol/l, respectively) (20).

The effects of HFD on peripheral tissue specific 11-β-HSD-1 expression (n=6 studies)

HFD increased corticosterone levels in visceral and epididymal fat after 18 weeks on HFD: 562 *vs* 477 ng/g in C57Bl/6J mice (16), and this effect of HFD was even more pronounced in C57Bl/6 J–11-β-HSD-1-KO mice (477 *vs* 159 ng/g, HFD *vs* control diet, respectively). However, another study (17) reported that HFD decreased 11-β-HSD-1 expression in adipose tissue, which was more pronounced in C57Bl/6 than in A/J mice, whereas HFD increased hepatic 11-β-HSD-1 expression (20). A fourth study found that HFD increased hepatic, epididymal, and visceral corticosterone levels in KKAy and ob/ob mice (21). The remaining 3 studies found effects on various genes (15), of genotype (C57Bl/6 *vs* GRβgeo +/+ (27)), and influence of time on the effectiveness of 11 β-HSD inhibition (29).

The effects of HFD on the central nervous system (n=5 studies)

Within the paraventricular nucleus of the hypothalamus (PVN), HFD did not affect CRH expression (2 studies: ref 18, 19), POMC expression (1 study: ref 27), or GR expression (1 study: ref 20). One study (22) found that HFD increased 11-β-HSD-1 expression transiently in the arcuate nucleus of the PVN after 2 weeks, but not after 18 weeks of the diet. Another study found that HFD did not

affect CRH expression in the amygdala in C57Bl/6 or A/J mice (19). Within the hippocampus, HFD did not alter GR expression (20) or 11-β-HSD-1 expression (22).

DISCUSSION

This systematic review demonstrates that data on the effects of HFD in mice on the basal activity of the HPA-axis are limited, and inconclusive. Circulating corticosterone concentrations in a total of only 20 studies were found to be increased, unchanged, or decreased. The relative energy contribution of fat in the HFD varied between 36-58%, 32-65% and 58-60%, respectively. In addition, data on the effects of HFD on 11-β-HSD-1 expression in the peripheral tissues and CRH and GR expression in the central nervous system (only 5 studies) were inconsistent. However, differences in mouse strains, housing and sampling conditions, and in the content and duration of the diets preclude simple comparisons of the effects of HFD on the activity of the HPA-axis, and accentuate the need for standardized evaluations to discern the effects of fat and diet-induced obesity on HPA-axis and the metabolic syndrome.

From an evolutionary point of view, the regulation of energy balance is integrated in the neurobiology of stress, i.e. into the regulation of the allostatic responses to environmental demands. Glucocorticoids are the main mediators of the stress response (33) and regulate fuel homeostasis by increasing feeding behavior when food becomes available (34). Within the hypothalamus, a rapid fine-tuned hormonal cross-talk exists between glucocorticoids and leptin, acting via leptin blockade of the glucocorticoid-induced, endocannabinoid-mediated suppression of excitation of the CRH expressing neurons. This provides a nutritional state-sensitive mechanism that integrates the neuroendocrine regulation of energy homeostasis and the stress response (35). HFD induced obesity is not only accompanied by higher leptin and insulin levels (15, 24) but also by altered diurnal patterns of leptin and insulin (24), which affect hypothalamic CRH suppression of HPA-axis.

Different housing conditions also affect the activity of the HPA-axis and might be considered as chronic social stress, which in turn influences the propensity to become obese. This is best illustrated by a recently proposed model of psychosocial stress in rats (a resident–intruder paradigm) linking allostatic load to metabolic disorders (36), and confirmed in mice (37). This model states that MetS and obesity can develop in presence of a HFD only when an environmental threat prevents active coping (fight/flight), but permits only a passive strategy. These experiments demonstrated that when both dominant and subordinate rodents were faced with a threatening situation, a similar overactive HPA-axis and hyperphagia was seen in both. However, dominants responded with an active coping style associated with sympathetic over activity in metabolic tissues that limited the development of obesity despite overfeeding, whereas subordinates responded with a passive helplessness strategy and, particularly when faced with a HFD, developed weight gain and obesity. Thus, the effects of stress and HFD appear to be less detrimental dependent on the ability of the individual to adequately cope with the stress, as a result of genetic predisposition, and/or social factors. These data accentuate the important role of psychosocial stress in modulating the individual vulnerability to weight gain, provided that the individual is fed an "unhealthy" high-fat diet.

When evaluating the impact of high fat feeding on adrenal axis function in mice, therefore, an appropriate study design is a prerequisite, and at least the following factors should be taken into account: first, the choice for a mouse strain that, upon high fat feeding, has previously shown

to provide a validated model for the development of specific features of the MetS, like obesity and insulin resistance. Second, standardization of content and duration of the diet. Third, standardization of acclimation period, housing conditions, and method for stress free sampling, and finally: the time of sampling. The relative contributions of each of these different factors can only be compared when study designs control for all these factors, except the one that is considered to be the intervention.

In conclusion, the effects of HFD on basal activity of the HPA-axis and its contribution in the propensity to become obese and develop other manifestations of the metabolic syndrome on a HFD are still unclear, but are at least time and context dependent. Proper standardization of these factors is critical in the evaluation of the role of the HPA-axis in further studies involving rodent models of the MetS.

REFERENCES

1. Isomaa B, Almgren P, Tuomi T, Forsen B, Lahti K, Nissen M, Taskinen MR, Groop L. Cardiovascular morbidity and mortality associated with the metabolic syndrome. *Diabetes Care* 2001; 24: 683–689
2. Reaven GM. Banting lecture 1988. Role of insulin resistance in human disease. *Diabetes* 1988; 37: 1595–1607
3. Gale EA. The myth of the metabolic syndrome. *Diabetologia* 2005; 48: 1679–1683
4. Dekker JM, Girman C, Rhodes T, Nijpels G, Stehouwer CD, Bouter LM, Heine RJ. Metabolic syndrome and 10-year cardiovascular disease risk in the Hoorn Study. *Circulation* 2005; 112: 666–673
5. Dallman F. Stress-induced obesity and the emotional nervous system. *Trends in Endocrinology and Metabolism* 2010; 3: 159-165
6. Warne JP. Shaping the stress response: interplay of palatable food choices, glucocorticoids, insulin and abdominal obesity. *Molecular and Cellular Endocrinology* 2009; 300: 137-14
7. Newell-Price J, Bertagna X, Grossman AB, Nieman LK. Cushing's syndrome. *Lancet* 2006; 367: 1605-1617
8. Dekkers OM, Biermasz NR, Pereira AM, Roelfsema F, van Aken MO, Voormolen JH, Romijn JA. Mortality in patients treated for Cushing's disease is increased, compared with patients treated for nonfunctioning pituitary macroadenoma. *Journal of Clinical Endocrinology & Metabolism* 2007; 92: 976-981
9. Anagnostis P, Athyros VG, Tziomalos K, Karagiannis A, Mikhailidis DP. Clinical review: The pathogenetic role of cortisol in the metabolic syndrome: a hypothesis. *Journal of Clinical Endocrinology & Metabolism* 2009; 94: 2692-2701
10. Müssiga K, Remerb T, Maser-Gluthc C. Brief review: Glucocorticoid excretion in obesity. *Journal of Steroid Biochemistry and Molecular Biology* 2010; 121: 589-593
11. Masuzaki H, Paterson J, Shinyama H, Morton NM, Mullins JJ, Seckl JR, Flier JS. A transgenic model of visceral obesity and the metabolic syndrome. *Science* 2001; 294: 2166-217
12. Cooper MS, Stewart PM. 11Beta-hydroxysteroid dehydrogenase type 1 and its role in the hypothalamus-pituitary-adrenal axis, metabolic syndrome, and inflammation. *Journal of Clinical Endocrinology & Metabolism* 2009; 94: 4645-4654
13. Herberg L, Kley HK. Adrenal function and the effect of a high-fat diet on C57BL/6J and C57BL/6J-ob/ob mice. *Hormone and Metabolic Research* 1975; 7: 410-415
14. Ziotopoulou M, Mantzoros CS, Hileman SM, Flier JS. Differential expression of hypothalamic neuropeptides in the early phase of diet-induced obesity in mice. *American Journal of Physiology* 2000; 279: 838-845
15. Moraes RC, Blondet A, Birkenkamp-Demtroeder K, Tirard J, Orntoft TF, Gertler A, Durand P, Naville D, Begeot M. Study of the Alteration of Gene Expression in Adipose Tissue of Diet-Induced Obese Mice by Microarray and Reverse Transcription-Polymerase Chain Reaction Analyses. *Endocrinology* 2003; 144; 4773-4782
16. Morton NM, Paterson JM, Masuzaki H, Holmes MC, Staels B, Fievet C, Walker BR, Flier JS, Mullins JJ, Seckl JR. Novel adipose

tissue-mediated resistance to diet-induced visceral obesity in 11 beta-hydroxysteroid dehydrogenase type 1-deficient mice. *Diabetes* 2004; 53: 931-938

17. Morton NM, Ramage L, Seckl JR. Down-regulation of adipose 11beta-hydroxysteroid dehydrogenase type 1 by high-fat feeding in mice: a potential adaptive mechanism counteracting metabolic disease. *Endocrinology* 2004; 145: 2707-2712
18. Bullen JW Jr, Ziotopoulou M, Ungsunan L, Misra J, Alevizos I, Kokkotou E, Maratos-Flier E, Stephanopoulos G, Mantzoros CS. Short-term resistance to diet-induced obesity in A/J mice is not associated with regulation of hypothalamic neuropeptides. *American Journal of Physiology – Endocrinology and Metabolism* 2004; 287: 662-670
19. Michel C, Duclos M, Cabanac M, Richard D. Chronic stress reduces body fat content in both obesity-prone and obesity-resistant strains of mice. *Hormones and Behavior* 2005; 48: 172-179
20. Morton NM, Densmore V, Wamil M, Ramage L, Nichol K, Bünger L, Seckl JR, Kenyon CJ. A polygenic model of the metabolic syndrome with reduced circulating and intra-adipose glucocorticoid action. *Diabetes* 2005; 54: 3371-3378
21. Alberts P, Rönquist-Nii Y, Larsson C, Klingström G, Engblom L, Edling N, Lidell V, Berg I, Edlund PO, Ashkzari M, Sahaf N, Norling S, Berggren V, Bergdahl K, Forsgren M, Abrahmsén L. Effect of high-fat diet on KKAy and ob/ob mouse liver and adipose tissue corticosterone and 11-dehydrocorticosterone concentrations. *Hormone and Metabolic Research* 2005; 37: 402-407
22. Densmore VS, Morton NM, Mullins JJ, Seckl JR. 11 beta-hydroxysteroid dehydrogenase type 1 induction in the arcuate nucleus by high-fat feeding: A novel constraint to hyperphagia? *Endocrinology* 2006; 147: 4486-4495
23. Luque RM, Kineman RD. Impact of obesity on the growth hormone axis: evidence for a direct inhibitory effect of hyperinsulinemia on pituitary function. *Endocrinology* 2006;147: 2754-2763
24. Kohsaka A, Laposky AD, Ramsey KM, Estrada C, Joshu C, Kobayashi Y, Turek FW, Bass J. High-fat diet disrupts behavioral and molecular circadian rhythms in mice. *Cell Metabolism* 2007; 6: 414-421
25. Chen H, Hansen MJ, Jones JE, Vlahos R, Anderson GP, Morris MJ. Detrimental metabolic effects of combining long-term cigarette smoke exposure and high-fat diet in mice. *American Journal of Physiology – Endocrinology and Metabolism* 2007; 293: 1564-1571
26. McClean PL, Irwin N, Cassidy RS, Holst JJ, Gault VA, Flatt PR. GIP receptor antagonism reverses obesity, insulin resistance, and associated metabolic disturbances induced in mice by prolonged consumption of high-fat diet. *American Journal of Physiology – Endocrinology and Metabolism* 2007; 293: 1746-1755
27. Michailidou Z, Carter RN, Marshall E, Sutherland HG, Brownstein DG, Owen E, Cockett K, Kelly V, Ramage L, Al-Dujaili EA, Ross M, Maraki I, Newton K, Holmes MC, Seckl JR, Morton NM, Kenyon CJ, Chapman KE. Glucocorticoid receptor haploinsufficiency causes hypertension and attenuates hypothalamic-pituitary-adrenal axis and blood pressure adaptions to high-fat diet. *FASEB Journal* 2008; 22: 3896-3907
28. Liu Y, Nakagawa Y, Wang Y, Liu L, Du H, Wang W, Ren X, Lutfy K, Friedman TC. Reduction of hepatic glucocorticoid receptor and hexose-6-phosphate dehydrogenase expression ameliorates diet-induced obesity and insulin resistance in mice. *Journal of Molecular Endocrinology* 2008; 41: 53-64
29. Véniant MM, Hale C, Komorowski R, Chen MM, St Jean DJ, Fotsch C, Wang M. Time of the day for 11beta-HSD1 inhibition plays a role in improving glucose homeostasis in DIO mice. *Diabetes, Obesity and Metabolism* 2009; 11: 109-117
30. Matsumoto S, Hashimoto K, Yamada M, Satoh T, Hirato J, Mori M. Liver X receptor-alpha regulates proopiomelanocortin (POMC) gene transcription in the pituitary. *Molecular Endocrinology* 2009; 23: 47-60
31. Warrier M, Hinds TD Jr, Ledford KJ, Cash HA, Patel PR, Bowman TA, Stechschulte LA, Yong W, Shou W, Najjar SM, Sanchez ER. Susceptibility to diet-induced hepatic steatosis and glucocorticoid resistance in FK506-binding protein 52-deficient mice. *Endocrinology* 2010; 151: 3225-3236
32. Czyzyk TA, Nogueiras R, Lockwood JF, McKinzie JH, Coskun T, Pintar JE, Hammond C, Tschöp MH, Statnick MA. kappa-Opioid receptors control the metabolic response to a

high-energy diet in mice. *FASEB Journal* 2010; 24: 1151-1159

33. de Kloet ER, Joëls M, Holsboer F. Stress and the brain: from adaptation to disease. *Nature Reviews Neuroscience* 2005; 6: 463-475
34. Akana SF, Strack AM, Hanson ES, Dallman MF. Regulation of activity in the hypothalamo-pituitary-adrenal axis is integral to a larger hypothalamic system that determines caloric flow. *Endocrinology* 1994; 135: 1125-1134
35. Di S, Malcher-Lopes R, Halmos KC, Tasker JG. Nongenomic glucocorticoid inhibition via endocannabinoid release in the hypothalamus: a fast feedback mechanism. *Journal of Neuroscience* 2003; 23: 4850-4857
36. van Dijk G, Buwalda B. Neurobiology of the metabolic syndrome: an allostatic perspective. *European Journal of Pharmacology* 2008; 585: 137-46
37. Bartolomucci A, Cabassi A, Govoni P, Ceresini G, Cero C, Berra D, Dadomo H, Franceschini P, Dell'Omo G, Parmigiani S, Palanza P. Metabolic consequences and vulnerability to diet-induced obesity in male mice under chronic social stress *PLoS One* 2009; 4: 4331