Published in final edited form as:

Physiol Behav. 2011 July 6; 103(5): 535–539. doi:10.1016/j.physbeh.2011.03.020.

METABOLIC SYNDROME AND NEUROMETABOLIC ASYMMETRY OF HIPPOCAMPUS IN ADULT BONNET MONKEYS

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Abstract

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Conflict of interest:

Dr Coplan receives grant support from GlaxoSmithKline, Pfizer, and Alexza Pharmaceuticals. He is on the Pfizer advisory board and gives talks for BMS, AstraZeneca, GSK, and Pfizer. Dr. Gorman is an employee of Comprehensive Neuroscience, Inc., a corporation that receives funding from the pharmaceutical industry for some of its projects. Dr. Owens receives research grants from Eli Lilly, Pfizer, GlaxoSmithKline, Merck, Lundbeck, Cyberonics, Ortho-McNeil Janssen and served as consultant for Pfizer, Lundbeck, Sepracor, Johnson & Johnson, Sanofi-Aventis, Forest Labs and as speaker s honoraria for GlaxoSmithKline. He is an inventor on the patent "A method to estimate transporter occupancy". Currently, Dr. Nemeroff serves on the Scientific Advisory Board for the American Foundation for Suicide Prevention (AFSP); NARSAD, PharmaNeuroboost and CeNeRx. He serves on the Board of Directors of AFSP; NovaDel Pharma, and Mt Cook Pharma, Inc. He owns equity or is stock holder in Revaax; NovaDel Pharma; CeNeRx, and PharmaNeuroboost. He is an inventor on the following patents: method and devices for transdermal delivery of lithium (US 6,375,990 B1) and method to estimate serotonin and norepinephrine transporter occupancy after drug treatment using patient or animal serum (US 7,148,027 B2). No biomedical financial interests or potential conflicts of interest are reported for Drs Abdallah, Mathew, Shungu, Mao, Smith, Kaufman, Banerji, Rosenblum, or Kral.

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Objective—Obesity is associated with the insulin resistance metabolic syndrome, postulated to be mediated by stress-induced alterations within the hypothalamic-pituitary-adrenal (HPA) axis. In adult bonnet macaques we examined relationships between components of the metabolic syndrome, hippocampal neurometabolic asymmetry, an indicator of negative affect, and juvenile cerebrospinal fluid (csf) corticotropin-releasing factor (CRF) levels obtained after stress exposure associated with maternal food insecurity and in controls.

Methods—Eleven adult male monkeys (seven with early life stress) who had undergone csf-CRF analyses as juveniles had magnetic resonance spectroscopic imaging (MRSI) of bilateral hippocampus, morphometry (body mass index, BMI; sagittal abdominal diameter, SAD) and determination of fasting plasma glucose and insulin as adults. Neurometabolite ratios included N-acetyl-aspartate as numerator (NAA; a marker of neuronal integrity) and choline (Cho; cell turnover) and creatine (Cr; reference analyte) as denominators.

Results—Elevated juvenile csf-CRF levels positively predicted adult BMI and SAD and were associated with right > left shift of NAA ratio within the hippocampus. Adult visceral obesity and insulin level correlated with right > left shift in hippocampal NAA concentrations, controlling for age and denominator.

Conclusion—Juvenile csf-CRF levels, a neuropeptide associated with early life stress, predict adult visceral obesity and hippocampal asymmetry supporting the hypothesis that metabolic syndrome in adults may be related to early life stress. Furthermore, this study demonstrates asymmetrical hippocampal alterations related to obesity.

Keywords

Corticotropin releasing factor; hippocampus; stress; metabolic syndrome; food insecurity; obesity

1. Introduction

Obesity and the metabolic syndrome are epidemic world-wide. The metabolic syndrome may be a consequence of neuroendocrine perturbations of the hypothalamic-pituitary-adrenal (HPA) axis typically associated with chronic stress .

Our previous work with bonnet macaque monkeys provides an animal model for studying the relationships between early life stress, and metabolic obesity . During their infant's first half-year, we expose their mothers to variable foraging demand (VFD), in which the difficulty of acquisition of ample food varies unpredictably, causing the offspring to show persistent abnormalities in HPA axis and central corticotropin-releasing factor (CRF) systems known to modulate stress response and affect . In the VFD model, we demonstrated positive relationships between juvenile cerebrospinal fluid (csf) CRF levels and subsequently measured body mass index, suggesting an interactive role of early experience and CRF dysregulation in the ontogeny of metabolic disorders .

In our colony of 250 laboratory-born normally-reared bonnet macaques receiving life-long standard monkey chow supplemented with fruit we found spontaneous increases in BMI associated with features of metabolic obesity and defined a primate metabolic syndrome using a composite score based on morphometry, insulin resistance, and serum lipid levels, analogous to clinical criteria .

CNS studies of obesity and energy balance have mainly focused on the ventromedial and lateral hypothalamus. However, BMI elevations and HPA axis disturbances may also be driven by limbic structures such as the hippocampus. Over the last decade many preclinical and clinical studies explored the role of the hippocampus in food intake and metabolic regulation (for review see). The hippocampus contains a high density of leptin and insulin

receptors, both of which are directly involved in metabolic regulation. Administration of each of these peptides has been shown to improve hippocampal-dependent functioning. In addition to the association between the hippocampus and eating behavior, human studies of hippocampal metabolic activities showed brain laterality in response to food craving and satiety signals. These studies indicate a correlation between eating behavior and increased right hippocampal activity. This is consistent with our findings in bonnet macaques of a positive association between body weight and right hippocampal N-acetyl-aspartate (NAA) – an amino acid considered reflective of neuronal density/functional integrity.

In the current study, we further explored our previously reported correlation between body weight, right hippocampal activity, and CRF dysregulation by using magnetic resonance spectroscopic imaging (MRSI) in an extended sample of bonnet monkeys. We tested whether relative elevations of juvenile csf-CRF, irrespective of early life stress status, would positively predict components of the metabolic syndrome as well as functional dominance of right > left hippocampal NAA in adult monkeys.

2. Methods

2.1 Subjects

Among an original group of 19 adult male Bonnet macaques (*Macaca radiata*) on which MRSI data had been collected, 11 with available bilateral spectral signals of hippocampus served as subjects. Males were selected to avoid potential cyclic fluctuations in gonadal steroids. Four of the 11 subjects had been raised under control conditions (LFD= low foraging demand) while 7 had been raised under the VFD condition. Mean monkey BMI (BMI= body weight in kg divided by crown-rump length in meters squared) was 35.2 ± 6.3 kg/m² and mean age was 9.0 ± 1.6 years (mean $\pm$ SD). Sagittal abdominal diameter (SAD), a measure of central or “visceral” adiposity, was measured during anesthesia for blood and csf sampling, as described by Kaufman et al. All monkeys are under careful veterinary supervision and are treated in accordance with the SUNY Downstate Medical Center- Institutional Animal Care and Use Committee. The Downstate Primate Colony is fully accredited by the Association for Assessment and Accreditation of Laboratory Animal Care – International (AAALAC-I).

2.2 Blood assays

Procedures for blood drawing and methods for assays are carefully described in reference. Plasma insulin (pmol/l) and blood glucose (mg/dl) were expressed as insulin-glucose ratio (IGR) as a measure of insulin resistance.

2.3 Cerebrospinal fluid (csf) analyses

CSF sampling was described in detail elsewhere. In summary, csf-CRF samples were drawn when the monkeys were 22-24 months of age. Sedation of subjects was achieved using 15mg per kg of intramuscular ketamine, followed by cisternal CSF sampling immediately after sedation. Assays for CRF were performed according to the methods described in Nemeroff et al.

2.4 Magnetic resonance spectroscopy imaging (MRSI)

Proton MRSI was performed under alphadolone/alphaxalone (Saffan) anesthesia using a 1.5 Tesla MRI applying the Duyn et al methods. Single voxels were placed bilaterally within the medial temporal lobe (MTL) (see fig. 1) and carefully aligned to represent the hippocampus. Neurometabolites were ascertained in vivo, using software specifically developed by Shungu et al. Neurometabolites included: N-acetyl-L-aspartate, (NAA), reflective of neuronal density/functional integrity; choline (Cho), a marker of cell membrane

turnover ; and the ubiquitous neurometabolite, creatine (Cr), the latter two being used as denominators to NAA, the numerator . Both NAA/Cho and NAA/Cr were used as the primary MRSI variables. In order to determine a measure of hippocampal NAA asymmetry, a right > left asymmetry index was derived from right/left hippocampus for NAA ratios. An index of 1 indicates symmetry between right and left hippocampus, index > 1 = right-sided dominance, and index < 1 = left-sided dominance.

2.5 Statistics

Monkeys with the bonnet macaque metabolic syndrome were compared to control subjects using independent t-tests. Advancing age was associated with elevated BMI ($r = 0.63$; $N = 11$; $p = 0.04$) and therefore age was controlled in regression analyses. Based on an overall uniform distribution of combined values, Pearson's parametric correlation matrix was applied to NAA/Cho asymmetry index and BMI, SAD, and plasma insulin and juvenile csf-CRF levels. To further validate the results, partial correlations between BMI, SAD, insulin and NAA/Cho difference values were determined, controlling in two separate multiple regression analyses for age and the two different rearing conditions (VFD versus LFD). Pearson's correlations were compared where appropriate using Fisher's r -to- z transformations. Significance was set at $p \leq 0.05$, two tailed.

3. Results

Juvenile csf-CRF concentrations correlated with adult BMI ($r = 0.62$; $N = 10$; $p = 0.05$), SAD (fig. 2) and right > left asymmetry of adult hippocampal NAA/Cho (fig. 3). The association with NAA/Cho ratio was limited to the right hippocampus ($r = 0.68$; $N = 10$; $p = 0.03$), but not left ($r = -0.08$; $N = 10$; $p = 0.82$), further suggesting a hippocampal neurometabolite asymmetry. Juvenile csf-CRF and adult right > left hippocampal NAA/Cr showed positive relationship without reaching statistical significance ($r = 0.48$; $N = 10$; $p = 0.16$).

BMI (fig. 4) and plasma insulin (fig. 5) correlated with right > left asymmetry of hippocampal NAA/Cr. Right > left asymmetry of hippocampal NAA/Cho was associated with increased BMI, whereas subjects with relatively low BMI exhibited an inverse relationship with left > right asymmetry of NAA/Cho ($r = -0.75$; $N = 11$; $p = 0.007$). The association between BMI and right > left NAA/Cho dominance remained when controlling for age and rearing type.

BMI and hippocampal NAA/Cho correlations were confined to the right hippocampus: the correlation between BMI and left NAA/Cho was $r = -0.03$ ($N = 11$; $p = 0.93$) but $r = 0.78$ ($N = 11$; $p = 0.005$) on the right (Fisher's r to z Chi square = 4.08; $p < 0.044$). The relationship between BMI and right NAA/Cr was also positive ($r = 0.63$; $N = 11$; $p = 0.039$) suggesting that right NAA increased with BMI independent of denominator. Left hippocampal NAA/Cr showed a border-line non-significant inverse relationship with BMI ($r = -0.44$; $N = 11$; $p = 0.18$; Fisher's r to z ; Chi square = 5.73; $p < 0.017$).

There were no significant differences between rearing groups in right/left NAA/Cho asymmetry index (LFD mean = 1.03 ± 0.43 versus VFD mean 1.11 ± 0.26 ; $t = 0.36$; $df = 9$; $p = 0.72$) or BMI (in kg/m^2) (LFD mean = 37 ± 7.7 versus VFD mean = 34 ± 5.9 ; $t = 0.50$; $df = 9$; $p = 0.63$).

Employing criteria for the bonnet macaque metabolic syndrome, we identified 5 monkeys qualifying as having the metabolic syndrome, based on elevation of three or more of: BMI, SAD, insulin, IGR and triglycerides . The remaining 6 monkeys had statistically significant

lower values on most variables and did not meet criteria for the metabolic syndrome, thus serving as controls in this respect (Table 1).

The metabolic syndrome subgroup exhibited significantly elevated right (3.44 ± 0.73 versus 2.46 ± 0.62 ; $t = 2.38$; $p = 0.04$), but not left NAA/Cho compared to the control animals. Although neither right nor left NAA/Cr differed between groups, a significantly greater degree of right > left asymmetry for NAA/Cr was observed (see Table 1). Collectively these data associate right > left NAA ratio in subjects with this primate metabolic syndrome. There were no significant association between rearing conditions and any of the measures of metabolic syndrome

4. Discussion

Cerebrospinal fluid concentrations of corticotropin-releasing factor drawn and analyzed when our male bonnet macaques were 22–24 months of age correlated with measurements of central obesity and neurometabolic asymmetry in mature adulthood (around 8–10 years of age). Right > left asymmetry, determined by right/left NAA ratio, was associated with high BMI and insulin levels in adults. The observed NAA hippocampal asymmetry indicates increased neuronal density and/or functional integrity in the right compared to left hippocampus.

Increased lines of evidence indicate an essential role for the hippocampus in differentiating food related cues, a function required for adequate energy regulation . Furthermore, hippocampal damage leads to increased food intake and weight gain (review:). The current study can not determine if the high BMI is a result of increased food intake, reduced energy expenditure or both. However, previous studies suggest an association between hippocampal dysfunction and increased food intake (review:). Furthermore, one study reported elevated metabolic activity in rats with complete hippocampal ablation . Interestingly, Davidson et al. noted a “vicious circle” of high-fat diet disrupting hippocampal functioning, a brain region needed for eating inhibitory control, leading to further increase of fat intake and obesity in line with recent work in diet-induced obese rats with impairment of hippocampal neurogenesis .

Our findings of right > left hippocampal NAA ratio asymmetry, in association with this primate metabolic syndrome, corroborate the previous animal and human studies findings of a potential role for hippocampal laterality in the development of obesity . Indeed, numerous studies have ascertained relationships between dietary obesity and fat intake, and hippocampal dysfunction (e.g.).

Limitations of our study are the small numbers of observations restricted to male monkeys in whom dominance patterns related to body size may have different effects than in females . Since the subjects were single-or pair-housed, having visual contact with other males, the role of social dominance versus size (expressed as BMI) cannot be determined in this study. We also had insulin level for only six subjects and we were unable to study food consumption in sufficient numbers of animals owing to variable housing conditions. Additionally, the use of ratios rather than absolute quantification of neurometabolites mandated multiple statistical analyses to confirm the findings, instead of a single correlation analysis. Furthermore, mechanisms underlying the relationships among CRF, body composition, insulin resistance and hippocampal asymmetry were not the object of the present study. Further imaging studies are necessary for comparison with neurohistology. The strengths of the current study include the emergence of obesity in a “naturalistic” environment in which bonnet macaques reared in social groups and – maintained on chow

diet in the absence of obesifying interventions such as dietary manipulation, restricted activities, or brain lesions.

Our bonnet macaque model, relating right > left hippocampal metabolism and central obesity may be particularly relevant to human metabolism and obesity due to similarities between the species in social structure and brain function. Right > left hippocampal NAA ratio asymmetry may reflect a supra-hypothalamic neural substrate of emotional distress that causes a disproportionate increase in central obesity, for example driving increased consumption of “comfort food”. These findings emphasize the need for early implementation of new approaches for preventing obesity and suggest novel pharmacological targets for treatment of metabolic obesity.

Acknowledgments

Research supported by: National Institute of Mental Health Grant MH 59990 and MH 58911 (JDC); National Alliance for Research on Schizophrenia and Depression Mid-Investigator Award (JDC); National Alliance for Research on Schizophrenia and Depression Young Investigator's Award (SJM); Psychiatric Institute Research Support Grant and by National Institute of Mental Health research fellowship T32-MH15144 (SJM); The Smart Family Foundation (JGK).

The authors thank Bruce Scharf, Douglas Rosenblum, Mohammad Arif, Shirm Baptiste, and Manuel de la Nuez. We also would like to thank Dr. Bruce McEwen for his invaluable contributions to this paper.

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Figure 1. Medial temporal lobe voxel placement and spectral readings from MRSI in the nonhuman primate

Medial temporal lobe (MTL) Voxel placement using 1.5 Tesla GE Magnetic Resonance Imager; in the right hand panel, encompassing the hippocampus, characteristic proton magnetic resonance spectral sequences are observed. NAA = N-Acetyl-Aspartate (a putative marker of neuronal integrity). Choline (Cho) which can be reflective of cell membrane turnover rate and creatine (Cr), a neurometabolite are used as denominator to NAA. MTL ratios for NAA/Cho and NAA/Cr were examined by hemisphere.

Figure 2. Relationship of juvenile csf-CRF to adult sagittal abdominal diameter
Juvenile csf-CRF concentrations correlated positively with sagittal abdominal diameter (SAD), a measure of visceral obesity (Pearson $s\ r = 0.74$; $N = 10$; $p = 0.013$)

Figure 3. Relationship of juvenile csf-CRF to adult hippocampal NAA asymmetry
 Adult right > left asymmetry of hippocampal NAA/Cho was associated with juvenile csf-CRF ($r = 0.64$; $N = 10$; $p = 0.048$). The asymmetry index was derived from right/left hippocampus for NAA ratio. An index of 1 indicates symmetry between right and left hippocampus; Index > 1 = right-sided dominance; Index < 1 = left sided dominance.

Figure 4. Relationship of body mass index to hippocampal NAA asymmetry

Right > left asymmetry of hippocampal NAA/Creatine was associated with BMI (Pearson $s\ r = 0.72$; $N = 11$; $p = 0.013$), whereas a left > right asymmetry of hippocampal NAA/Creatine was inversely related to plasma insulin.

Figure 5. Relationship of plasma insulin to hippocampal NAA asymmetry

Right > left asymmetry of hippocampal NAA/Creatine was positively correlated with adult plasma insulin levels (Pearson $s\ r = 0.87$; $N = 6$; $p = 0.024$), whereas a left > right asymmetry of hippocampal NAA/Creatine was inversely related to plasma insulin.

Comparison of subjects with bonnet macaque metabolic syndrome (N = 5; Met-Syn) versus control (N = 6).

Table 1

	Met-Syn Group		Control Group		t-value	df	p
	Mean ± SD	N	Mean ± SD	N			
b-Glucose (mg/dl)	73 ± 17.4	4	83 ± 9.2	6	-1.18	8	.271
p-Insulin (pmol/l)	41 ± 22.0	3	14 ± 3.9	3	2.04	4	.111
IGR	0.49 ± .18	3	0.16 ± .03	3	3.08	4	.037
p-Cholesterol (mg/dl)	113 ± 18.3	4	110 ± 18.8	5	.19	7	.856
p-Triglyceride (mg/dl)	81 ± 73.0	4	70 ± 47.1	6	.28	8	.787
p-HDL (mg/dl)	45 ± 2.5	4	34.7 ± 7.3	6	2.76	8	.025
p-LDL (mg/dl)	51 ± 14.2	4	60 ± 24.0	6	-.65	8	.535
Cholesterol/HDL	2.50 ± .46	4	3.26 ± .91	6	-1.52	8	.166
SAD (cm)	13.9 ± 2.1	5	10.7 ± 1.9	6	2.64	9	.027
BMI (kg/m ²)	41 ± 3.1	5	30 ± 3.6	6	5.13	9	.001
Right > Left NAA/Cr	1.13 ± .20	5	0.84 ± .21	6	2.30	9	.047

Abbreviations: Bonnet macaque metabolic syndrome (Met-Syn); Blood (b); Plasma (p); Insulin glucose ratio (IGR); Sagittal abdominal diameter (SAD); Body mass index (BMI).