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Psychological distress during lactation period induces long term effects in a sex-dependent manner in mice

Anna Capasso*

Department of Pharmacy, University of Salerno, Italy

Abstract

Early-perinatal events exert relevant effects on several metabolic and neurohumoral parameters of the adult life, but scarce information are available on the sex effects on the neonatal programming. Adult CD-1 non-handled female (NHF) mice weigh less than non-handled males (NHM), have a lower incremental area under the curve (iAUC) than NHM after glucose loading, but not after insulin loading; have higher plasma uric acid, and lower plasma total choleste rol and high density lipoprotein (HDL (C), while plasma triglycerides and creatinine are not different. Neonatal handling (10 min of maternal deprivation plus subcutaneous injection of saline solution) daily, for the first 21 days of life, induces overweight, hyperglycemia, and elevation in triglycerides in CD1 adult male mice, whereas uric acid, creatinine, HDL (C), total cholesterol, insulin and glucose iAUC are not significantly changed. At any age studied, neonatal handling does not produce any significant changes in females within the time windows considered in our experimental conditions. These results indicate that the onset of sex differences may be very precocious, and that sex is an independent variable for the developmental programming.

Abbreviations: NHM (non-handled males); NHF (non-handled females); HM (handled males); HF (handled females); iAUC (incremental area under the curve); HPA axis (hypothalamic-pituitary-adrenal axis)

Introduction

Prevalence and severity of overweight-obesity is increasing and this alarming augmentation includes childhood populations worldwide [1]. The control of body weight depends on many factors including early events of life [2] such as malnutrition [3]. However, few studies suggest that other events during lactation could have a role in metabolic programming [4-6]. In male mice, neonatal handling, which includes psychological distress (10 min of maternal separation), associated with a mild painful stimulus for the whole lactation period, produces long term overweight associated with significant variations in lipid and glucose homeostasis, immunological and hormonal status [6-8].

To be men or women is one of the most important determinants of human health, [9]. This raises the possibility that sex can influence the response to neonatal events in mammals, notwithstanding only few reports are available on this topic. In particular, at the 28th postnatal week, mean body weight and fasting insulin levels are significantly increased in the rats of both sexes perinatally fed with a specific n-6/n-3 fat acid diet, while the systolic blood pressure and serum triglycerides are elevated in male adults only [10]. Sex-related vulnerability in brain development are also described in humans: boys are found to acquire their circadian sleeping rhythm later than girls, and to sleep significantly shorter periods at night, whereas this gender-related pattern is not found for eating-feeding rhythms [11]. Moreover, neonatal treatment with indomethacin of human preterm infants has long term consequences on cognitive performance in school-aged boys but not in school-aged girls [12]. Finally, 70% of CD-1 male mice neonatally treated with glutamate develop type-2 diabetes mellitus and glucose intolerance, whereas the incidence of diabetes in females is consistently lower than in males (about 24%) and starts later [13].

Therefore, it is of interest to address the question whether neonatal handling that induces metabolic derangement and overweight in males [6] affects females as well.

Differences due to sex

Recent studies indicate that NHM and NHF CD1 mice show interesting metabolic differences [14-16]. Some of these differences (higher body weight and HDL (C) level in males) were already described [13]. Further differences emerge from recent studies [14-16]. In particular, NHM have a higher iAUC, and glucose peaks after glucose loading than NHF, whereas NHF have higher uric acid level than NHM. Creatinine, fasting glucose and insulin loading do not show significant sex differences. Lipid levels are sexual dimorphic in numerous species including humans [17]. Indeed, some sex differences have been also described in glucose homeostasis [18]; interestingly, some of them start at birth [19]. These differences in glucose homeostasis could reside in the effect of estrogens, because they seem to be implicated in glucose-induced insulin secretion probably through the closure of K^+ ATP channels [20].

NHF have higher levels of uric acid than NHM. Females may increase uric acid production because the acid is produced by xanthine-oxidase, an enzyme that, in endothelial cells, is induced by physiological estrogens concentrations [21]. Additionally, males and females could "use" differently this endogenous antioxidant, since in general cells gathered from male gender are more susceptible to oxidative stress than "female" cells [22].

Correspondence to: Anna Capasso, Department of Pharmacy, University of Salerno, Italy, E-mail: annacap@unisa.it

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At variance of many species including humans [23], creatinine levels are similar in both sexes suggesting that these differences could be species-specific.

Finally, at 30 days of age, NHF and NHM have a similar nociceptive response when hot-plate test is considered [14-16].

Differences due to sex and handling

Neonatal handling produces sustained effects in adult males, whereas it does not seem to induce consistent variation of the developmental trajectory in females [14-16]. In particular, body weight, nociception, fasting plasma glucose levels, and triglycerides are significantly varied in adult males and not in females [14-16]. At variance of previous data [6], at weaning, i.e., at the end of the handling period HM weight is significantly lower than NHM. This data may be depended on the higher number of animals used in this study. This could be of some importance because a low birth size is associated with glucose intolerance and the development of insulin-independent diabetes mellitus [24] suggesting that the body weight at the end of suckling period could be a sensitive predictor for lipid and glucose metabolic alterations in male adults. The sex differences observed here are in line with those described by *Nagata, et al.* [13], who reported that neonatal administration of glutamate induces the development of type-2 diabetes mellitus in 70% of CD-1 male mice, whereas the incidence of diabetes in females is notably less (about 24%) and starts later [13]. The "resistance of female" could be due to a particular phenotype of rodent females versus alteration in glucose homeostasis [25]. However, sex differences in glucose homeostasis have been described by many authors in different experimental and clinical settings [19,26-34].

Sex has a relevant effect also on lipids, because triglycerides plasma level of HM is significantly increased *versus* NHM as previously reported [6], but not in HF *versus* NHF. However the increase in total cholesterol levels in the present experiment does not reach the statistical significance, which was previously found [6].

Neonatal handling does not influence kidney function in our experimental conditions [14-16], as reflected by plasma creatinine, and does not induce significant changes of plasma uric acid levels in adults, whereas it is a sensitive index of neonatal programming in humans, further confirming the species-specificity of the process.

As previously described [6], at 30 days of age HM present an increase in nociceptive response threshold, and this seems to occur *via* the opioid system enhanced function, since this effect is prevented by treatment with naloxone, an antagonist of opioid receptors; naloxone effect was evidenced in both conditions, i.e., administered either just during the lactation period, and then tested at the 30th day of life, or administered just 20 minutes before testing, at the 25th and 45th day of life [8,35]. Once again, in the present study HF at the 30th day of life did not show consistent differences in the nociceptive threshold from NHF. After puberty, sexual differences in painful response in rodents have been described [36-38], and probably these differences were sustained by estrogens [39]. Thus, females appear to be resistant to neonatal handling in comparison with males. Actually, it is not possible to know whether the metabolic alterations in females will appear at an older age in comparison with males, and further experiments are being performed. One of the main principles of developmental programming is the concept of the critical time-window [40] thus it is possible that males and females can differ in critical time-windows.

The experimental protocol was not designed to evaluate the mechanisms that underlie the differences [14-16]. However, previous studies showed than HM have 200-300% higher plasma levels of corticosterone, and adrenocorticotropin, accompanied by a higher pituitary adrenocorticotropin and lower hypothalamic adrenocorticotropin and corticotrophin-releasing-hormone levels, versus NHM, thus suggesting the importance of the correct functioning of hypothalamic-pituitary-adrenal (HPA) axis and its feed-back mechanisms in neonatal programming [6,7,14-16]. The importance of said mechanisms is further confirmed by the fact that neonatal administration of an antisense anti-proopiomelanocortin, which is able to prevent pituitary proopiomelanocortin synthesis, and therefore also adrenocorticotropin and β-endorphin release, prevents the modification of developmental trajectory induced by neonatal handling as well, and restores/protects the physiological hormonal feed-back mechanisms in male mice [7,14-16]. The role of HPA axis in programming has been recently reviewed [41]. Importantly, estrogen administration in the first day of life can affect the HPA axis [42] and this could be important in view of the estrogen role in controlling glucose homeostasis [33].

Summary

In conclusion, a mild but repeated psychological distress (daily maternal separation) plus a mild but repeated painful stimulus (sham injection) during lactation period induce long term effects in a sex-dependent manner [14-16]. The dimorphic effect in glucose and lipid homeostasis following neonatal handling is novel and of interest in view of the fact that changes in developmental trajectory has been obtained using both mild psychological distress and painful stimulus [14-16]. Although caution must be used to extrapolate these data to humans, because developmental trajectory differs among the species [43], these data suggest that we should develop different strategies for females and males in order to prevent adult diseases in mammals. This hypothesis is somehow confirmed by a recent paper [44], which shows that the prevalence of the metabolic syndrome in U.S. adolescents aged 12-17 years for the period 1999-2004 was higher among males (6.7%) than females (2.1%).

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