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Consequences of a double hit of stress during the perinatal period and midlife in female rats: Mismatch or cumulative effect?

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ABSTRACT

The interplay between experiences during critical developmental periods and later adult life is crucial in shaping individual variability in stress coping strategies. Exposure to stressful events in early life has strongly programs an individual's phenotype and adaptive capabilities. Until now, studies on programming and reversal strategies in early life stress animal models have been essentially limited to males. By using the perinatal stress (PRS) rat model (a model more sensitive to aging changes) in middle-aged females, we investigated the behavioral and endocrine responses following exposure in later life to an unpredictable chronic mild stress (uCMS) condition for six weeks. PRS by itself accelerated the ageing-related-disruption in the estrous cycle and led to reductions in the levels of estradiol. It also reduced motivational and risk-taking behavior in later life, with PRS females being characterized by a reduction in self-grooming in the splash test, in the exploration of the light compartment in the light/dark box test and in the time spent eating a palatable food in the novelty-induced suppression feeding test. PRS females showed impaired regulation of plasma glucose and insulin levels following a glucose challenge, with a hyperglycemic phenotype, and disrupted feedback of the HPA axis after acute stress with respect to controls. Remarkably, all PRS-induced alterations were modified by exposure to the uCMS procedure, thus resulting in a disease-dependent intervention; controls were not affected by uCMS, except for a slight and transient reduction in body weight, while PRS females displayed a reduced body weight gain for the entire duration of the uCMS procedure. Interestingly, the effects of uCMS on PRS females were still observed up to two months after its termination and the females displayed heightened rhythms of locomotor activity and enhanced sensitivity to reward with respect to controls exposed to uCMS. Our findings indicate that many parameters of the PRS female adult phenotype are shaped by both early and later life experiences in a non-additive way. As a consequence, early stressed individuals may be programmed with a more dynamic phenotype than non-stressed individuals.

1. Introduction

Adverse experiences in life can affect adult health either by cumulative damage over time in adulthood or by experiences during sensitive periods such as perinatal life, adolescence, and aging (McEwen, 2016). Early life events related to maternal care in animals, as well as parental care in humans, play a powerful role in later mental and physical health, as demonstrated by studies of adverse childhood experiences and other recent works (Maccari et al., 2017; Tang et al., 2014). Exposure to stressful events such as disrupted parental care and poor socio-economic status or undernutrition during sensitive periods of life, can lead to the development of several neurological, metabolic, and

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neuroendocrine abnormalities in the individual, a phenomenon known as programming (Barker, 1995), which has been shown extensively in the past two decades in human as well as animal studies (Maccari et al., 2017; Nemeroff, 2004; Seckl, 2008).

A well characterized animal model of early programming is the perinatal stress (PRS) model in the rat (Maccari et al., 1995), in which exposure to prenatal stress and altered maternal behavior, programs a life-long disruption in the activity and feedback of the hypothalamus-pituitary-adrenal (HPA) axis (Vallée et al., 1999) as well as an impairment of glucose metabolism, with an increased vulnerability to type 2-diabetes (Vallée et al., 1996; Lesage et al., 2004). These endocrine alterations are associated with a profound fragmentation of sleep architecture and disruption of circadian rhythms (Dugovic et al., 1999; Mairesse et al., 2013), and altered emotional behaviors (behavioral response to novelty), from infancy (Vallée et al., 1999; Zuena et al., 2008; Laloux et al., 2012).

Environmental and pharmacological interventions at different ages and sensitive periods can reverse the adverse programming induced by PRS. Enhancement of maternal behavior during the first few days of life is a key step for reversal of PRS-induced alterations. Indeed, early adoption (Maccari et al., 1995), although not late adoption (Barbazanges et al., 1996), early handling (postpartum stress of the mother, Koehl et al., 1997), or postpartum treatment with the oxytocinergic agonist carbetocin (Gatta et al., 2018), can normalize the hyperactivity and feedback of the HPA axis in PRS animals. During adolescence, environmental enrichment can also normalize HPA axis activity, as well as emotional behavior of the PRS offspring (Morley-Fletcher et al., 2003). In adulthood, several neurobehavioral alterations observed in this animal model, including sleep, are corrected by chronic treatment with antidepressants (Morley-Fletcher et al., 2011; Mairesse et al., 2013; Marrocco et al., 2014), or activation of the oxytocinergic system with carbetocin (Mairesse et al., 2015). Exposure to perinatal stress has a sex-dependent effect on emotional behavior in the elevated-plus maze, with higher levels of risk-taking behavior in the exploration of the open arm in PRS females when compared to males, which explore less (Zuena et al., 2008). In contrast, alterations of HPA axis activity, circadian rhythms, and reward-dependent behavior are observed in both sexes at the adult stage. Interestingly, PRS reduces estradiol levels in adult females, thus shaping the alteration in hedonic sensitivity to palatable food. Moreover, supplementation of PRS females with estradiol hormones fully reverses this profile (Reynaert et al., 2016).

The interplay between experiences during sensitive developmental periods and the later adult environment seems to be a crucial factor in shaping individual variability in stress coping strategies. Two main hypotheses have been formulated to address the interaction between stresses in early and later life. The more traditional hypothesis is the “cumulative stress” or “multiple hit” hypothesis, where aversive experiences early in life predispose individuals to be more vulnerable to aversive challenges later in life (Nederhof and Schmidt, 2012). Accordingly, the effects of environment are cumulative and result in an increased allostatic load, which would increase the likelihood of developing a disease. Alternatively, the second hypothesis, known as the “match/mismatch” hypothesis, states that stressful experiences early in life trigger adaptive processes, thereby rendering an individual better adapted to aversive challenges later in life (Nederhof and Schmidt, 2012). Since stress is essential in life as “you can’t live with it, you cannot live without it” (Lupien and Lepage, 2001), it is necessary to understand the interplay of several stressful events, occurring in different sensitive periods of life. Interestingly, research findings indicate that there may be multiple sensitive time periods, depending upon the domains of development assessed (Armstrong et al., 2006), and evidence does not identify the early years as the only sensitive time period within which a significant influence upon development can occur. In line with this reasoning, aging, with its associated changes in hormonal production, is a sensitive period of increased vulnerability to stress-related disorders (Bartsch and Wulff, 2015).

The aim of the present study, then, was to investigate in the PRS model the interplay between PRS and later chronic stress in middle-aged females, an age window that is poorly studied. To our knowledge, research studies on programming and effects of chronic stress in adult life, in animal models of early life stress, have been too frequently limited to males, with some exceptions made for studies from our group (Louvart et al., 2009) and others (Lukkes et al., 2017; Panetta et al., 2017; Mueller and Bale, 2008; Baker and Bielajew, 2007). Here, we showed that the PRS female adult phenotype is shaped by both early and later life experiences in a non-additive way, confirming the “match/mismatch” hypothesis, with the exception of body weight gain and locomotor activity.

2. Material and Methods

2.1. Animals and perinatal stress procedure

All experiments followed the rules of the European Communities Council Directive 2010/63/EU.

2.1.1. Animals

In total, 40 Nulliparous female Sprague-Dawley rats, weighing approximately 250 g, were purchased from a commercial breeder (Harlan, France). Animals were housed at constant temperature (22 ± 2 °C) and under a regular 12 h light/dark cycle (lights on at 8:00 am). A vaginal smear using Endocrine serum (NaCl 0.9%) was performed on the morning following mating with an experienced male. The day on which the smear was sperm positive was considered to be embryonic day 0 (E0). After mating, pregnant females were individually housed with *ad libitum* access to food and water at constant temperature (22 °C ± 2 °C), and under a regular 12 h light/dark cycle (light on at 8:00 am). On E11, pregnant females were randomly assigned to restraint stress or control groups (20 per group). Control females were left undisturbed, with an exception made for weighing one time per week in order to follow gestation.

2.1.2. Perinatal stress protocol

Pregnant females group was subjected to a restraint stress procedure according to a standard protocol (Maccari et al., 1995; Morley-Fletcher et al., 2003). From day 11 of pregnancy until delivery, pregnant female rats were subjected to three stress sessions daily (45 min each), during which they were placed in plastic transparent cylinders with a conical extremity and exposed to bright light or were left undisturbed (control dams). Stress sessions were conducted during the light phase (between 9:00 am and 5:00 pm) with a minimum interval of 2 h between each stress session. The local ethical committee approved the gestational restraint procedure. Maternal behavior was monitored 24 h/day during the first seven post-partum days. Constant monitoring was performed with small infrared cameras placed on the animal cage rack where lactating females were located in their cages. Within each observation period, the behavior of each mother was scored every min from post-partum day 1 to day 7 (60 observations/h with 2 h of observation per day, one h before lights off and one h after lights on). The active behavior of the mother (nursing behavior, grooming, licking, carrying pups) was scored and the data obtained were expressed as percentages with respect to the total number of observations. In the present study, only female offspring from dams presenting a stress-reduced maternal behavior (with a cutoff below 40% of maternal care in the PRS group *vs.* a cutoff above 60% of maternal care in the control group), and from litters of 10–14 rats with a similar number of males and females, were used. Since gestational stress induces a reduction of maternal behavior, we refer to the whole procedure as perinatal stress (PRS, prenatal and postnatal effect). Offspring were weaned 21 days after birth and left undisturbed until the beginning of the experiments. Only two female siblings were taken from each litter to minimize any litter effect (Chapman and Stern, 1979).