Neurobiology of Stress 6 (2017) 22–30

Contents lists available at ScienceDirect

Neurobiology of Stress

journal homepage: http://www.journals.elsevier.com/neurobiology-of-stress/

Neonatal corticosterone administration in rodents as a tool to investigate the maternal programming of emotional and immune domains

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ARTICLE INFO

Article history:
Received 25 September 2016
Received in revised form
21 December 2016
Accepted 26 December 2016
Available online 28 December 2016

Keywords:
Neonatal experiences
Corticosterone
Maternal programming
Experimental models

ABSTRACT

Neonatal experiences exert persistent influences on individual development. These influences encompass numerous domains including emotion, cognition, reactivity to external stressors and immunity. The comprehensive nature of the neonatal programming of individual phenotype is reverberated in the large amount of experimental data collected by many authors in several scientific fields: biomedicine, evolutionary and molecular biology. These data support the view that variations in precocious environmental conditions may calibrate the individual phenotype at many different levels. Environmental influences have been traditionally addressed through experimental paradigms entailing the modification of the neonatal environment and the multifactorial (e.g. behaviour, endocrinology, cellular and molecular biology) analysis of the developing individual's phenotype. These protocols suggested that the role of the mother in mediating the offspring's phenotype is often associated with the short-term effects of environmental manipulations on dam's physiology. Specifically, environmental manipulations may induce fluctuations in maternal corticosteroids (corticosterone in rodents) which, in turn, are translated to the offspring through lactation. Herein, I propose that this mother-offspring transfer mechanism can be leveraged to devise experimental protocols based on the exogenous administration of corticosterone during lactation. To support this proposition, I refer to a series of studies in which these protocols have been adopted to investigate the neonatal programming of individual phenotype at the level of emotional and immune regulations. While these paradigms cannot replace traditional studies, I suggest that they can be considered a valid complement.

1. Neonatal environmental variations calibrate the individual phenotype

The influences of the neonatal environment on individual development have been documented in countless studies conducted in a variety of species (Bateson et al., 2004; Gluckman et al., 2005): water fleas (Fisk et al., 2007; Latta et al., 2007), birds (Groothuis and Carere, 2005), mice (Macrì et al., 2011; Lyons and Macrì, 2011), rats (McEwen, 2000; Meaney, 2010; Plotsky and Meaney, 1993; Pryce et al., 2002, 2005), guinea pigs (Hennessy et al., 2006; Sachser et al., 2013; Siegeler et al., 2013), and primates (Lyons and Parker, 2007; Petrullo et al., 2016; Parker and Maestripieri, 2011). Preliminary considerations bridging neonatal experiences with individual long-term adjustments originally derived from the field of psychoanalysis wherein Freud proposed that adult neuroses build upon infantile experiences (Freud, 1918). These original hypotheses have been further supported by epidemiological data demonstrating that the rearing environment exerted persistent long-term effects on individual phenotype. For example, several authors demonstrated that infant abuse, neglect or parental loss, are associated with increased long-term vulnerability to major depressive disorder (Heim and Nemeroff, 1999, 2001). Epidemiological data and retrospective studies have been corroborated by prospective experiments conducted in laboratory animals. Specifically, the interactions between neonatal experiences and adult phenotype have been investigated through variable approaches generally entailing the systematic variation of neonatal conditions and the evaluation, in developing individuals, of selected phenotypes (Liu et al., 1997; Francis et al., 2002; Ruedi-Bettschen et al., 2005; Coutellier et al., 2008; Macrì et al., 2008; Macrì and Wurbel, 2007). The original studies investigated the

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http://dx.doi.org/10.1016/j.ynstr.2016.12.001

effects of different lengths of mother-offspring separations on the development of the hypothalamic-pituitary-adrenocortical (HPA) axis. The latter represents the principal system involved in the regulation of individual reactivity to stressors and in a plethora of evolutionarily adaptive responses like survival, foraging, fighting, mating, and reproduction (Sapolsky, 2004).

In the attempt to demonstrate that adverse neonatal conditions may increase the risk to develop HPA-related disturbances, several authors addressed – in rodents – the long-term effects of prolonged periods of maternal separation (3–6 h per day) applied during the early stages of postnatal life (Ruedi-Bettschen et al., 2005; Macrì et al., 2004, 2008; Ruedi-Bettschen et al., 2004a, b). These studies showed that maternal separation resulted in a persistent increase in individual HPA reactivity in terms of adrenocorticotropic hormone (ACTH), corticosterone, and hypothalamic corticotropin-releasing factor (CRF) (Francis et al., 2002). Beside modulating physiological reactivity, neonatal adversities resulted in alterations in behavioural phenotypes dependent on the regulation of the HPA axis: e.g. fear, anxiety, and cognition (Macrì et al., 2004; Huot et al., 2004; Yang et al., 2016). Additional studies demonstrated that maternal separation may also influence the development of other biological systems involved in survival and defensive responses. For example, Loria and collaborators (Loria et al., 2013) demonstrated that maternal separation applied during the first two weeks of life persistently modified the regulation of the autonomic nervous system. Thus, adult rats exposed to maternal separation exhibited persistent increases in norepinephrine contents in renal cortex, inner and outer medulla, spleen and adrenals (Loria et al., 2013). Just as these experiments demonstrated that neonatal adversities may increase individual sensitivity to later experimental challenges, so also other studies demonstrated that a nurturing environment may reduce individual behavioural and physiological reactivity to stressors. The pioneering studies demonstrating the beneficial effects of favourable neonatal environments have been performed in the 1950's by Weininger (Weininger, 1954; Weininger et al., 1954) and Levine (Levine, 1957; Levine et al., 1957). These authors independently demonstrated that neonatal stimulating environments may promote the development of the HPA axis and favour long-term resilience, the capability to rapidly adjust to repeated stressors (Feder et al., 2009). For example, Weininger demonstrated that gently stroking rat pups for 10 min per day during the first three weeks of life resulted in a long-term reduction in physiological damage and behavioural fearfulness (Weininger, 1954; Weininger et al., 1954). Likewise, Levine demonstrated that a similar experimental procedure conducted in neonate rats exerted analogous effects on adrenal sensitivity (Levine, 1957). Finally, several authors demonstrated that brief maternal separations (15 min per day) during the early stages of neonatal life resulted, in adulthood, in reduced reactivity to psychophysiological stressors (Macrì et al., 2004; Levine, 1957; Fernandez-Teruel et al., 2002; Meaney et al., 2000).

The aforementioned studies represent a very limited portion of the thousands of studies performed within this field of investigation. These studies have been detailed in comprehensive reviews to which the reader is referred (Pryce et al., 2005; Andersen, 2015; Pryce and Feldon, 2003). Within the framework of the present manuscript, it is important to emphasize that the modulatory role exerted by the neonatal environment on the adult phenotype has been regarded from several different angles: evolutionary biology, biomedicine, and molecular biology.

1.1. The evolutionary adaptive perspective: why are neonatal influences so relevant to the developing individual?

One of the core hypotheses bridging early experiences with the adult phenotype poses that the developing individual uses neonatal cues to adaptively adjust its phenotype according to the specific demands encountered in adulthood (Bateson et al., 2004; Gluckman et al., 2005). The freshwater crustacean *Daphnia* represents a paradigmatic example. These water fleas may develop a protective "helmet" early in life depending on the environmental conditions. Specifically, in the presence of a predator odour, *Daphnia* develops a helmet providing survival advantages. However, helmet patterning comes at the expense of remarkable energetic costs. Therefore, individual adaptive success depends on the presence or absence of predators early in life and on the likelihood that neonatal cues match adult environmental conditions. Thus, just as the presence of the helmet begets advantages in the presence of predators, its patterning may result in adaptive disadvantages should environmental conditions vary (Bateson et al., 2004). Analogous considerations have been translated to rodents (Liu et al., 1997; Sachser et al., 1994) and humans (Wells, 2007a, 2007b; Hales and Barker, 2001). Several authors suggested that maternal behaviour in rodents may represent a source of information for the developing individual which, in turn, exploits this information to adaptively adjust its phenotype (Liu et al., 1997; Wurbel, 2001). For example, Liu et al (1997) proposed that the persistent reduction in the activation of the HPA axis, observed in adult offspring reared to dams exhibiting spontaneously elevated levels of maternal care, reflected adaptive adjustments in which the developing individual attempted to match the maternal environment (for a review, see also (Macrì and Wurbel, 2006)). This hypothesis rests upon two fundamental assumptions: (i) the niche inhabited by the developing offspring is similar to the niche inhabited by the mother; (ii) the mother represents a crucial source of information during a developmental stage characterised by elevated phenotypic plasticity. These assumptions can be valid in rats. Thus, although the Norway rat inhabits a large variety of environments, it has a sympatric ecology and in adulthood is likely to inhabit the same niche in which it has grown. Furthermore, during the first highly plastic weeks of postnatal life, rats and mice have very limited access to the surrounding environment whereby they are generally kept in a quiet, stable and safe nest. During this stage, in which rats have a very limited motility, the mother constitutes the only source of information regarding the surrounding environment. Shortly after weaning rats are capable of navigating their environment and survive independently of the mother. This mother-offspring information transfer has been often framed within the field of maternal programming of offspring's phenotype (see also (Wurbel, 2001)).

While addressing the adaptive significance of the mother-offspring information transfer, it is important to emphasize that the largest portion of this manuscript is devoted to the study of laboratory rodents, which are characterised by immaturity at birth and rapid postnatal growth. Yet, different species are characterised by remarkably different life-history strategies (number of offspring, precocial or altricial development, parental investment, r or K selection (Pianka, 1970)). Variations in life-history strategies may considerably alter the modalities of mother-offspring information transfer. For example, Groothuis and collaborators (Henriksen et al., 2011; Groothuis et al., 2005) conducted a consistent series of studies in birds, an altricial species in which the embryonic development occurs outside the maternal body, in an enclosed environment (the egg) which is sensitive to maternal hormones. Notwithstanding remarkable differences in the mother-offspring information transfer mechanisms, Groothuis and collaborators

observed that egg hormones may adjust the developing offspring's phenotype in accordance with environmental challenges (Groothuis et al., 2005). Thus, the possibility to investigate precocial and altricial experimental models may disclose important evolutionary commonalities in species characterised by different life-history strategies.

1.2. The biomedical perspective: neonatal influences on the development of individual pathology

As reported above, the HPA axis is involved in the regulation of a series of biological functions including emotions, physiology, foraging, mating and reproduction (Sapolsky, 2004). Thus, alterations in HPA axis development have been reported to contribute – to name a few – to psychiatric disturbances (Heim et al., 1997), metabolic alterations and eating disorders (Mocking et al., 2013; Het et al., 2015; Lavagnino et al., 2014). Thus, the possibility to influence HPA axis development has represented a valuable tool to investigate the biological determinants of a plethora of disturbances and to develop experimental models of pathologies upon which designing innovative therapeutic approaches (Pryce et al., 2005; Andersen, 2015; Brummelte et al., 2006; Carola et al., 2008; Nestler et al., 2002; Zoratto et al, 2011, 2013). For example, the observation that maternal neglect related to increased risk of major depression (Heim and Nemeroff, 2001; Heim et al., 2008) translated in preclinical studies in which different forms of infantile neglect have been modelled in laboratory animals. Whilst the original studies have been conducted in monkeys (Harlow et al., 1964; Rosenblum and Paully, 1987), most experiments have been performed in rats and mice (e.g (Andersen, 2015; Zoratto et al., 2011).). Specifically, developing rats and mice, separated in infancy from their mothers for extended periods of time, have been tested for their depressive-like phenotypes (Andersen, 2015; Macrì and Laviola, 2004; Leventopoulos et al., 2009; Ruedi-Bettschen et al., 2004a, b). These studies demonstrated that environmental adversity often resulted in an upregulated HPA reactivity and in a behavioural phenotype isomorphic to depressive disorders (Leventopoulos et al., 2009; Ruedi-Bettschen et al., 2004a, b). Thus, adult rats exposed to prolonged maternal separations in infancy displayed anhedonia (unwillingness to work in order to obtain a palatable reward), impaired motivation for appetitive stimuli, reduced locomotion, alterations in circadian rhythms and increased anxiety. Other studies leveraged the influence of the neonatal environment to design experimental paradigms of human psychiatric disorders like anxiety (Heim and Nemeroff, 1999, 2001; Carola et al., 2008; Coutellier et al., 2009) and post-traumatic stress disorder (Heim et al., 1997).

Beside emotions, the long-term influences of the precocious environment have been investigated in the field of metabolic disturbances. The thrifty phenotype hypothesis constitutes one classical example (Wells, 2007a, b; Hales and Barker, 2001). This hypothesis has been developed following the observation of an elevated incidence of type-2 diabetes in a large cohort of Dutch individuals that, during the late stages of gestation, have been exposed to undernourishment due to an embargo incurred during World War II (Ravelli et al., 1976, 1999; Jackson et al., 1996). The authors proposed that the onset of type-2 diabetes reflected a long-term adaptive process through which the organism attempted to regulate its metabolism in accordance with the specific demands of the environment (Hales and Barker, 1992). Briefly, according to the thrifty phenotype hypothesis, precociously undernourished subjects would develop a metabolism capable of capitalising and maximising the scant available resources. Yet, in conditions of abundant food resources, a parsimonious phenotype would be disadvantageous whereby it would not be capable to proficiently handle the available energetic resources. This hypothesis has also been recently confirmed in preclinical studies adopting a precocious protein restriction protocol (Qasem et al., 2012; Plagemann, 2006).

The aforementioned studies highlight the importance of the study of precocious programming of individual phenotype within the field of biomedicine. These studies may first offer prospective experimental support to these hypotheses and then aid the generation of innovative therapeutic approaches. A thorough understanding of the link between neonatal experiences and the development of individual emotional phenotypes may inform the design of counselling activities devoted to emotional management and parental advice. For example, Draper and collaborators (Draper et al., 2009) highlighted the importance of early preventive interventions, involving parents and teachers, in the management of early-onset mental disturbances. Simpson and Catling (2016) recently reviewed clinical evidence supporting a link between traumatic birth experiences and the onset of mental health disturbances, and the efficacy of different therapeutic interventions. In the absence of unequivocal conclusive evidence, the authors reported that postnatal counselling may beget considerable benefits (Simpson and Catling, 2016). Ultimately, although many studies are still needed to detail the maternal programming of emotional and physiological phenotypes, these studies may in the long-term influence societal decisions.

1.3. The molecular biology perspective: fundamental mechanisms contributing to the maternal programming of the adult phenotype

One additional aspect that has intrigued many authors is constituted by the identification of the fundamental determinants of the interaction between neonatal life conditions and the adult offspring phenotype. Thus, several authors identified some of the fundamental mechanisms underlying the conversion of transient neonatal environmental variations into persistent adjustments. Within this field, several authors proposed that the maternal programming of offspring phenotype occurs through epigenetic mechanisms involving histone acetylation, DNA methylation, and glucocorticoid receptor expression (Weaver et al., 2004). The original studies investigating the maternal programming of HPA reactivity observed that elevated levels of maternal care resulted in a persistent increase of glucocorticoid receptor (GR) expression in the hippocampus (Liu et al., 1997). Maternally-mediated alterations in GR expression resulted in a reduced sensitivity to glucocorticoids. These investigations have then been paralleled by additional studies attempting to identify the molecular substrates favouring this mother-offspring information transfer. Epigenetics, herein broadly defined as the “branch of biology which studies the causal interactions between genes and their products” (Waddington, 1942), constituted the most valid candidate. Specifically, DNA methylation and histone modifications represent two of the most important molecular mechanisms modulating gene expression (see (Dudley et al., 2011) for a detailed review). Weaver and collaborators (Weaver et al., 2004) started detailing the epigenetic determinants of the maternal programming of offspring's phenotype by demonstrating that increased GR receptor expression was associated with decreased DNA methylation and increased histone acetylation at specific sites within the hippocampal GR promoter. These epigenetic modulations favour GR transcription through a facilitation of the activity of the transcription factor NGF1A (Weaver et al., 2007). These variations have been proposed as the fundamental mechanisms bridging variations in maternal care and the programming of the HPA axis in the adult offspring (Meaney, 2001, 2010).

2. Which maternal factors exert programming roles?

In the previous paragraphs, I briefly outlined few of the theoretical and experimental fields tackled by the maternal programming of offspring phenotype. Although many authors adopted these experimental protocols with diverse aims, one aspect is still unanswered: what aspects of mother-offspring interaction influence the development of the individual phenotype? In the following paragraphs I will attempt to address this question focussing on studies conducted in laboratory rodents.

2.1. Maternal milk composition

Maternal milk and its nutrients constitute one of the most direct mediators of the mother-offspring information transfer. Specifically, a growing body of literature is currently devoted to understanding the role played by human milk oligosaccharides (HMO), a family of glycans abundant in maternal milk and capable of influencing the development of gut microbiota, immune function, and neurocognitive development (Bode, 2012). The role exerted by HMOs on individual development has been demonstrated in clinical and preclinical studies. For example, Wang and Brand-Miller reviewed epidemiological evidence indicating that, compared to formula-feeding, breast-feeding may beget cognitive advantages (Wang and Brand-Miller, 2003). This retrospective evidence received preclinical experimental support by studies showing that the administration of specific nutrients of maternal milk improved learning and memory in laboratory rats (Sakai et al., 2006). Additionally, experimental evidence supports the possibility that environmental stressors may influence the composition of gut microbiota (Tannock and Savage, 1974) and that the latter may affect the former (Bangsgaard Bendtsen et al., 2012). Finally, Tarr and collaborators (Tarr et al., 2015) observed that the dietary supplementation of selected HMOs reduced anxiety-like behaviour in adult mice. Thus, although this field of investigation is still at its inception, it is tenable to suggest that maternal milk composition may be an important modulator of environment-mediated maternal programming of individual phenotype. Thus, the previous considerations support the plausibility of the hypothesis that maternal milk composition may vary in response to environmental conditions and that alterations in its content may regulate individual behaviour. However, in the absence of consolidated literature in this specific field of investigation, I believe that future studies are needed to detail the relationship between maternal milk composition and adaptive phenotypic programming.

2.2. Maternal behaviour

Maternal behaviour, i.e. the way in which rodent mothers take care of their offspring, has traditionally constituted the principal candidate. Maternal behaviour generally refers to the entire ethogram exhibited by rat and mouse mothers when in contact with their offspring (see (Stern, 1996, 1997)). Briefly, maternal care consists of a series of patterns ranging from passive postures, in which the mother is providing minimal care, to active postures (licking, grooming, arched-back nursing, LGABN postures), in which the mothers provide maximal levels of care. During LGABN bouts, beside providing milk, dams groom and lick their offspring to facilitate excretion of urine and faeces (Stern, 1996, 1997). The possibility that maternal care modulates individual development has been originally hypothesised based on neonatal handling studies (Liu et al., 1997). Thus, brief periods of maternal separation have been repeatedly reported to result in increased maternal care and in a subsequent reduction of HPA reactivity in the adult progeny (Liu et al., 1997; Macrì et al., 2004). Meaney and his collaborators extended these observations by demonstrating that, beside experimentally induced alterations in active nursing, also spontaneous differences in maternal care influenced offspring development. Specifically, the authors first subdivided a large population of rats into high and low caring mothers and then followed the individual development of their offspring. Resting upon this experimental paradigm, the authors demonstrated that rats born and reared to high LGABN mothers showed reduced emotionality, physiological stress reactivity, and improved coping strategies (Caldji et al., 1998, 2003; Francis et al., 1999). Furthermore, to demonstrate that maternal influences were independent of prenatal factors (e.g. pregnancy hormones), the authors performed a series of cross-fostering studies in which rats born to low-caring mothers were transferred to high-caring dams and vice versa. These studies further corroborated the non-genomic modulatory role exerted by maternal behaviour on the developing offspring's phenotype (Francis et al., 2002).

Although this evidence offers a robust support to the possibility that maternal behaviour constitutes a crucial determinant of individual phenotype, other studies reported conflicting evidence. Specifically, several studies demonstrated that absolute levels of maternal care and the reactivity of the HPA axis in adulthood may dissociate (Macrì et al., 2008, 2004, 2007). For example, we performed a maternal separation study in which different groups of rats were exposed to non-handling (the cages were untouched for the first two weeks of life, apart from provision of food and water), postnatal handling (15-min daily separations for the first two weeks of life) and maternal separation (4-hr daily separations) (Macrì et al., 2004). We observed that, compared to non-handling and maternal separation, postnatal handling reduced HPA reactivity and behavioural fearfulness in the adult offspring. Yet, absolute levels of maternal behaviour were different between early handling and non-handling, but indistinguishable between postnatal handling and maternal separation mothers. Ultimately, maternal behaviour and individual development of stress and fear responses dissociated. Independent evidence that maternal care does not constitute the primary mechanism through which dams "program" the individual phenotype has been obtained by Tang and collaborators (Akers et al., 2008; Tang et al, 2003, 2006; Tang and Reeb, 2004). Specifically, the authors adopted a neonatal split-litter design in which half of the litter was daily and briefly (3 min) exposed to a novel environment while the other half remained in the home cage. Within the scopes of the present manuscript, the relevance of these studies resides in the fact that all littermates were reared to the same mother but exposed to differential environmental conditions. Exposure to novelty modulated the individual phenotype – at the level of social behaviour, HPA reactivity and cognitive abilities – independently of maternal care (Tang et al, 2003, 2006; Tang and Reeb, 2004).

2.3. Maternal corticosteroids

Based on the evidence reported above, although maternal care can partly mediate individual development, other postnatal non-genomic maternal factors are likely to calibrate phenotypic adjustments in the progeny. Together with other authors (Brummelte et al., 2006; Casolini et al., 2007; Catalani et al., 2011, 2000, 1993; Pawluski et al., 2009), I suggest that maternal corticosterone may represent a valid candidate capable of influencing individual development. The main considerations upon which this hypothesis rests are the following: plasma corticosterone concentrations fluctuate in response to environmental challenges (D'Amato et al., 1992; Deschamps et al., 2003; Huot et al., 2002); corticosterone concentrations in maternal milk parallel corticosterone concentrations in plasma (Catalani et al., 1993; Pawluski et al., 2009;

D'Amato et al., 1992; Deschamps et al., 2003; Huot et al., 2002; Macrì et al., 2009); corticosterone is transferred from the dam to the offspring through maternal milk (Macrì et al., 2009); exogenous corticosterone administration to lactating dams adjusts individual development (Brummelte et al., 2006; Catalani et al, 1993, 2000; Macrì et al., 2009).

As anticipated above, the HPA axis constitutes one of the primary systems devoted to responding to imminent and perceived threats (Sapolsky, 2004). Defensive responses are mediated via several hormones rapidly released in the peripheral circulation following the emergence of a given threat. Corticosterone, one of the principal hormones of the HPA axis, mediates energy expenditure and catabolic functions (Sapolsky, 2004; McEwen, 1998). In rodents, plasma corticosterone concentrations have been shown to rise in response to numerous experimental challenges like exposure to novelty (Morley-Fletcher et al., 2003), isolation (Gavrilovic and Dronjak, 2005), predators (Vendruscolo et al., 2006), food restriction (Stamp et al., 2008) and many others. Notwithstanding pregnancy- and lactation-related specificieties, plasma corticosterone elevations can be readily observed in lactating dams. Specifically, lactating rodents have been frequently reported to exhibit smaller corticosterone elevations compared to non-lactating females (Lightman and Young, 1989; Shanks et al., 1999). Yet, environmental challenges, like exposure to novel bedding (D'Amato et al., 1992) or predator odour (Deschamps et al., 2003), have been shown to consistently elevate circulating concentrations of corticosterone in lactating mouse and rat dams. The influence of precocious adversities on individual HPA reactivity has also been observed in studies in which experimental stressors have been applied during gestation. For example, Knaepen and collaborators (Knaepen et al., 2013) demonstrated that repeated exposure to restraint stress in rat mothers resulted in reduced concentrations of corticosteroid binding globulin (CBG), a transport protein capable of modulating the bioavailability of glucocorticoids. Specifically, CBG binds corticosteroids thereby inhibiting their activity on target organs: therefore, reduced concentrations of CBG may ultimately result in increased availability of free (unbound) corticosteroids (Crino et al., 2014).

The possibility that variations in maternal corticosterone concentrations are paralleled in offspring's plasma has been documented in a study in which we exogenously supplemented corticosterone to mouse lactating dams (Macrì et al., 2009). In this study, we first administered corticosterone to lactating dams in the drinking water and then evaluated corticosterone concentrations in the developing offspring. Therein we observed that maternal hormonal concentrations were linearly reflected in offspring's plasma corticosterone concentrations. Analogous results have been obtained by independent authors (Yorty et al., 2004). The maternal supplementation protocol has also been highly informative with respect to the possibility that variations in circulating corticosterone concentrations directly influenced individual development (Macrì et al., 2011; Catalani et al., 2011; Sullivan and Holman). The seminal work in this field has been performed by Catalani and collaborators (Catalani et al., 1993). In a series of studies, the authors demonstrated that adult rats reared to dams supplemented with low doses of corticosterone showed reduced stress reactivity and behavioural fearfulness, and increased memory performance (reviewed in (Catalani et al., 2011)). Furthermore, they observed that reduced HPA reactivity was associated with increased hippocampal expression of glucocorticoid receptors (Catalani et al., 2000). Adopting analogous experimental protocols, we showed that low doses of neonatal corticosterone improved cognitive performance in an attentional set-shifting task (Macrì et al., 2009), and reduced behavioural anxiety in a novelty approach–avoidance conflict test in adult mice (Macrì et al., 2007). Whilst these studies demonstrated that low doses of neonatal corticosterone reduce later HPA reactivity, other studies showed that high doses of neonatal corticosterone may exert opposite effects. For example, Brummelte and collaborators (Brummelte and Galea, 2010b; Brummelte et al., 2006) observed that male rats reared to dams exposed to elevated levels of corticosterone during lactation showed increased behavioural fearfulness and anxiety measured in the open field and in the resistance to capture respectively. These findings were also paralleled by a remarkable decrease in cell proliferation in the dentate gyrus (Brummelte et al., 2006).

Beside regulating stress physiology, precocious administration of corticosterone has been shown to persistently adjust the reactivity of the immune system. For example, Yorty et al. (2004) demonstrated that maternal exposure to elevated doses of corticosterone affected offspring response to an immune challenge in mice. Specifically, the authors demonstrated that neonatal supplementation of corticosterone to the maternal drinking water affected offspring capability to survive a herpes simplex virus infection (Yorty et al., 2004).

3. Heuristic advantages of experimental models based on neonatal corticosterone administration

In the previous paragraphs, I proposed that natural elevations in plasma corticosterone – in response to the environmental challenges encountered by the dam – may translate to the progeny through lactation and ultimately influence their phenotypic development. Beside its theoretical relevance with respect to the maternal programming of adult phenotype, these observations may constitute the grounding upon which powerful experimental paradigms in preclinical biomedical research can be developed. Specifically, exogenous corticosterone administration constitutes a valid experimental paradigm whereby it affords full controllability both in terms of doses and timing of administration. Furthermore, since corticosterone can be easily supplemented in the drinking water, the administration procedure is only minimally invasive. As mentioned above, the HPA axis contributes to the calibration of a large number of domains; therefore, the possibility to regulate its development through a non-invasive pharmacological administration may beget remarkable advantages in several fields of investigation. In the following section, I will discuss how this evidence has been applied to emotional and immune domains.

3.1. Neonatal corticosterone administration and emotional disturbances

The influence of neonatal adversities on the development of emotional regulations has been demonstrated in several different studies conducted in humans (Heim and Nemeroff, 1999, 2001), primates (Harlow et al., 1964), rats (Pryce et al., 2005) and mice (Macrì and Laviola, 2004). Most of these studies rested upon rearing protocols in which neonate individuals were exposed to adverse environmental conditions. To give few examples, in preclinical models, neonatal adversities have been mimicked through prolonged maternal separations, isolation, access to variable foraging demands, or exposure to fearful stimuli like predators, their odours, or aggressive unrelated males. These procedures have been shown to result, in adulthood, in considerable alterations in emotional domains. For example, Lee and colleagues observed, in rats, that repeated maternal separations (3-hr per day) during the first two weeks of life resulted in increased indices of depression: increased helplessness and anxiety, and reduced hippocampal concentrations of serotonin (Lee et al., 2007). Adopting an analogous experimental protocol, Lippmann and collaborators showed that neonatal maternal separation results, in the long-term, in reduced

locomotion, increased behavioural stereotypies and physiological HPA activation in response to restraint stress (Lippmann et al., 2007). Ruedi-Bettschen and collaborators (Ruedi-Bettschen et al., 2005) adopted an early deprivation protocol in which neonate pups were separated for extended periods of time from their dams and littermates. This procedure resulted, in the long-term, in increased anhedonia measured as the reduced willingness to work to obtain a palatable reward (Ruedi-Bettschen et al., 2005). However, while some studies related neonatal adversities with the onset of behavioural phenotypes reminiscent of depressive-like symptoms, other studies, adopting analogous experimental designs, failed to obtain the same results. For example, several studies reported that extended periods of maternal separation during the early stages of life did not result in major phenotypic variations in the adult offspring (Macrì et al., 2004, 2008; Macrì and Wurbel, 2006). One of the hypotheses potentially explaining the inconsistent results relates to the possibility that even very minor variations in the experimental procedure may have differential effects on the dams, which is then reflected in a differential adaptation in the adult offspring. For example, Ruedi-Bettschen and collaborators (Ruedi-Bettschen et al., 2005) reported that early deprivation procedures exerted radically different effects on the adult offspring if applied during the dark or the light phase of the circadian rhythm.

Conversely, maternal corticosterone administration is easily standardised and likely to beget more consistent experimental outcomes. Based on the possibility that environmental adversities are reflected in maternal circulating corticosterone and that this is directly involved in the phenotypic programming of the offspring, several authors adopted corticosterone supplementation protocols to develop experimental designs aimed at evaluating the precocious origins of emotional disturbances (Macrì et al., 2011; Brummelte et al., 2006; Zoratto et al, 2011, 2013; Brummelte and Galea, 2010a; Brummelte and Galea, 2010b). For example, Brummelte and collaborators (Brummelte et al., 2006) observed that post-partum administration of corticosterone resulted in depressive like behaviours both in the dams and in the adult offspring.

In an independent set of experiments, we combined maternal corticosterone supplementation in the drinking water with dietary tryptophan depletion to develop an experimental model of depression in mice (Zoratto et al, 2011, 2013). These preclinical studies rested upon clinical evidence indicating that depression was associated both with exposure to environmental stressors and to a dysfunctional regulation of the serotonergic system (Caspi et al., 2003). Based on this evidence, we aimed at reproducing these aetiological factors in preclinical models by interfering with the natural development of the HPA axis and of the serotonergic system. While the former was attained through corticosterone supplementation, the latter was mimicked through the administration – to lactating dams – of a tryptophan deficient diet. Tryptophan is an essential amino acid necessary for the synthesis of serotonin. In accordance with our predictions, we observed that adult offspring reared to dams exposed to these treatments showed an aberrant regulation of the serotonergic system (Zoratto et al., 2013) and of HPA reactivity (Zoratto et al., 2011). Furthermore, they showed behavioural and neurochemical abnormalities isomorphic to depressive symptoms: increased anhedonia and anxiety, and increased hypothalamic concentrations of brain derived neurotrophic factor (Zoratto et al., 2013).

3.2. Neonatal corticosterone administration and immunity

The immune system constitutes an additional target upon which neonatal experiences may exert persistent influences. Levine and his group performed a series of pioneering studies demonstrating the direct and bimodal link between corticosterone activity and immune responses. Specifically, they demonstrated that repeated stressors, in the form of restraint, suppressed the "development of clinical and histologic signs of experimental allergic encephalomyelitis" (EAE) (Levine et al., 1962a, b); Levine and collaborators also showed that the same stressful procedure was sufficient to prevent the relapses in a relapsing-remitting experimental model of EAE. The authors proposed that the regulatory effects of stressors on the onset and course of EAE are mediated via corticosterone: specifically, the stress-induced hypersecretion of corticosterone has been proposed to exert immunosuppressive effects thereby mitigating the autoimmune phenomena typical of EAE (Levine and Saltzman, 1987). These effects have been proposed to relate to the fact that elevations in circulating corticosteroids may suppress cell-mediated immune responses through a direct action at the level of T cells (Hu et al., 1993; Wick et al., 1993). Complementary to these data, Levine and colleagues (Levine et al., 1962a, b) also demonstrated that corticosterone deficiency, obtained through adrenalectomy, exacerbated the consequences of EAE. These data constitute the grounding upon which evaluating the effects that the neonatal environment exerts on long-term immune responses. Within this framework, Laban and colleagues (Laban et al., 1995) reported that neonatal handling, previously reported to reduce HPA reactivity to stressors (Liu et al., 1997; Macrì et al., 2004), aggravated the symptoms of EAE. Furthermore, Meagher and colleagues (Meagher et al., 2010) reported that repeated brief (15-min per day) and long (3-hr per day) episodes of maternal separation during infancy increased viral load and decreased viral clearance in response to Theiler's murine encephalomyelitis virus infection in adolescent and adult offspring. Importantly, in this study, both brief and long periods of maternal separation resulted, in the long-term, in a blunted corticosterone response. This final aspect is in contrast with part of available literature whereby long periods of maternal separation have often been reported to increase, rather than decrease corticosterone reactivity. Thus, this study highlights several critical aspects: (i) neonatal experiences may adjust individual immune reactivity; (ii) these effects are likely mediated via alterations in corticosterone reactivity; (iii) the effects of neonatal experiences of corticosterone reactivity are not consistent across different studies.

Based on these considerations, it is tenable to propose that experimental models based on the neonatal administration of glucocorticoids may favour data consistency and reproducibility, and beget theoretical advantages in the field of neonatal calibration of the immune system. As already reported above, Yorty and collaborators addressed the relationship between neonatal corticosterone administration and the development of immune responses (Yorty et al., 2004). While this study addressed the effects of maternal corticosterone on short-term immune reactivity in the offspring (Yorty et al., 2004), we performed an independent study in which we evaluated how neonatal corticosterone administration affected the reactivity of the immune system in adult offspring (Macrì et al., 2007). Specifically, we evaluated the capability of adult individuals to respond to an infection with *Brucella melitensis*. Thus, two weeks after infection, we quantified the residual colony forming units in the spleens of adult offspring reared to control mothers or mothers supplemented with low doses of corticosterone. In this experiment, we observed that neonatal corticosterone administration improved immune reactivity by reducing the number of colony forming units (Macrì et al., 2007). Adopting a similar procedure, Bakker and collaborators investigated the link between dexamethasone (a glucocorticoid receptor agonist) and the development of immune responses in rats (Bakker et al., 2000). The authors administered dexamethasone between postnatal day 1 and 3 to Wistar rats and then evaluated its effects on the symptom

progression in EAE. The authors observed that neonatal dexamethasone aggravated symptoms severity and that this effect was associated with a reduction in corticosterone reactivity to experimental challenges (Bakker et al., 2000). Although the results reported in the aforementioned studies (Macrì et al., 2007; Bakker et al., 2000) may appear conflicting, it should be highlighted that while (Macrì et al., 2007) evaluated the reactivity of the immune system to a direct infection (Bakker et al., 2000), evaluated the reactivity to autoimmune phenomena. Thus, both studies suggest that neonatal exposure to glucocorticoids may potentiate immune reactivity in adulthood: yet, while, on the one hand, such potentiation is functional to responding to the active bacterial infection, on the other hand, it begets an aggravated phenotype in response to an experimental model of autoimmunity. Ultimately, these two studies may be considered two sides of the same coin further strengthening the fundamental significance of developmental plasticity: the adaptive or maladaptive significance of phenotypic adjustments should be evaluated within the specific context in which such phenotype is exhibited.

4. Conclusions

In this manuscript I proposed that neonatal corticosterone administration may constitute a central experimental protocol potentially informing the developmental programming of adult phenotype. I believe that this experimental protocol may complement traditional studies, entailing classical environmental manipulations like handling, maternal separations, or provision of rearing environments characterised by variable foraging demands (Coutellier et al., 2008, 2009; Macrì and Wurbel, 2007; Rosenblum and Paully, 1984). The main limitation of corticosteroid supplementation models resides in their pharmacological nature, which neglects the environment encountered by the experimental subjects and limits the full HPA response (involving CRF, pro-opiomelanocortin, ACTH, and corticosteroid receptors, to name a few) to corticosterone.

Yet, notwithstanding these limitations, corticosterone administration protocols afford a repeatable procedure in which exposure to corticosteroids can be fully controlled in terms of dose and timing. Furthermore, in the light of the numerous studies associating individual development with neonatal circulating corticosteroids, these procedures allow the isolation of corticosteroid-mediated effects from other contributing variables. However, although the approach proposed herein rests upon a single hormone, corticosterone has a relatively large-spectrum effect on individual physiology. Specifically, corticosteroids bind both mineralocorticoid (MR) and glucocorticoid receptors, which are abundantly expressed in several peripheral and central target organs (Joels et al., 2008). Therefore, the specificity of the effects of corticosterone needs to take into consideration the biological role of GR and MR. Future studies shall thus contemplate the use of selective GR and MR agonists and antagonists (Ye et al., 2014; Koizumi and Yada, 2008; Myers and Van Meerveld, 2010). Ultimately, rather than proposing neonatal corticosterone as an alternative to classical paradigms, I suggest that this procedure shall represent their valid complement.

Acknowledgements

I wish to warmly thank Giovanni Laviola for continuous feedback on this topic. During manuscript writing, I received support from the European Community's Seventh Framework Programme (FP7/2007–2013) under grant agreement n 603016 (Project MATRICS), from the Italian Ministry for Research and Education, project “Understanding how attachment styles, personality traits, and their biological determinants regulate individual adaptation to living in small confined groups” and from the Italian Ministry of Health, project Progetto Giovani Ricercatori: “Unraveling the mystery of Alzheimer's Disease-related synaptic degeneration”. This paper reflects only the authors' views and the European Union is not liable for any use that may be made of the information contained therein.

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