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**DOI**

[10.3109/10253890.2015.1064890](https://doi.org/10.3109/10253890.2015.1064890)

**Publication date**

2015

**Document Version**

Final published version

**Published in**

Stress - the International Journal on the Biology of Stress

**License**

Article 25fa Dutch Copyright Act

[Link to publication](#)

**Citation for published version (APA):**

Yam, K. Y., Naninck, E. F. G., Schmidt, M. V., Lucassen, P. J., & Korosi, A. (2015). Early-life adversity programs emotional functions and the neuroendocrine stress system: the contribution of nutrition, metabolic hormones and epigenetic mechanisms. *Stress - the International Journal on the Biology of Stress*, 18(3), 328-342. <https://doi.org/10.3109/10253890.2015.1064890>

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## REVIEW ARTICLE

# Early-life adversity programs emotional functions and the neuroendocrine stress system: the contribution of nutrition, metabolic hormones and epigenetic mechanisms\*

Kit-Yi Yam<sup>1</sup>, Eva F. G. Naninck<sup>1</sup>, Mathias V. Schmidt<sup>2</sup>, Paul J. Lucassen<sup>1</sup>, and Aniko Korosi<sup>1</sup><sup>1</sup>Swammerdam Institute for Life Sciences, Center for Neuroscience, University of Amsterdam, XH Amsterdam, The Netherlands and <sup>2</sup>Department Stress Neurobiology and Neurogenetics, Max Planck Institute of Psychiatry, Munich, Germany**Abstract**

Clinical and pre-clinical studies have shown that early-life adversities, such as abuse or neglect, can increase the vulnerability to develop psychopathologies and cognitive decline later in life. Remarkably, the lasting consequences of stress during this sensitive period on the hypothalamic–pituitary–adrenal axis and emotional function closely resemble the long-term effects of early malnutrition and suggest a possible common pathway mediating these effects. During early-life, brain development is affected by both exogenous factors, like nutrition and maternal care as well as by endogenous modulators including stress hormones. These elements, while mostly considered for their independent actions, clearly do not act alone but rather in a synergistic manner. In order to better understand how the programming by early-life stress takes place, it is important to gain further insight into the exact interplay of these key elements, the possible common pathways as well as the underlying molecular mechanisms that mediate their effects. We here review evidence that exposure to both early-life stress and early-life under-/malnutrition similarly lead to life-long alterations on the neuroendocrine stress system and modify emotional functions. We further discuss how the different key elements of the early-life environment interact and affect one another and next suggest a possible role for the early-life adversity induced alterations in metabolic hormones and nutrient availability in shaping later stress responses and emotional function throughout life, possibly via epigenetic mechanisms. Such knowledge will help to develop intervention strategies, which gives the advantage of viewing the synergistic action of a more complete set of changes induced by early-life adversity.

**Environmental factors present during early-life and their role in the development of psychopathology later in life**

Early-life (EL) is a critical period for brain development. Exposure to adverse experiences during this sensitive period is associated with lasting changes in later brain structure and function (Lupien et al., 2009; Teicher et al., 2012) as well as with an increased vulnerability to develop psychopathologies, cognitive deficits and anxiety disorders later in life (Abe et al., 2007; Bale et al., 2010; Gershon et al., 2013; Glover, 2011; Kroupina et al., 2012; Loman et al., 2010). Several epidemiologic studies strongly support a direct association between early-life stress (ELS) exposure and the development of psychopathology in adulthood, as shown for example by childhood sexual abuse (Danese & Tan, 2014; Heim et al., 2010; Maselko et al., 2011; McGowan et al., 2009; Neigh

**Keywords**

Early-life stress, emotional functions, epigenetic mechanisms, HPA axis, leptin, nutrition

**History**

Received 15 January 2015  
Revised 18 May 2015  
Accepted 25 May 2015  
Published online 11 August 2015

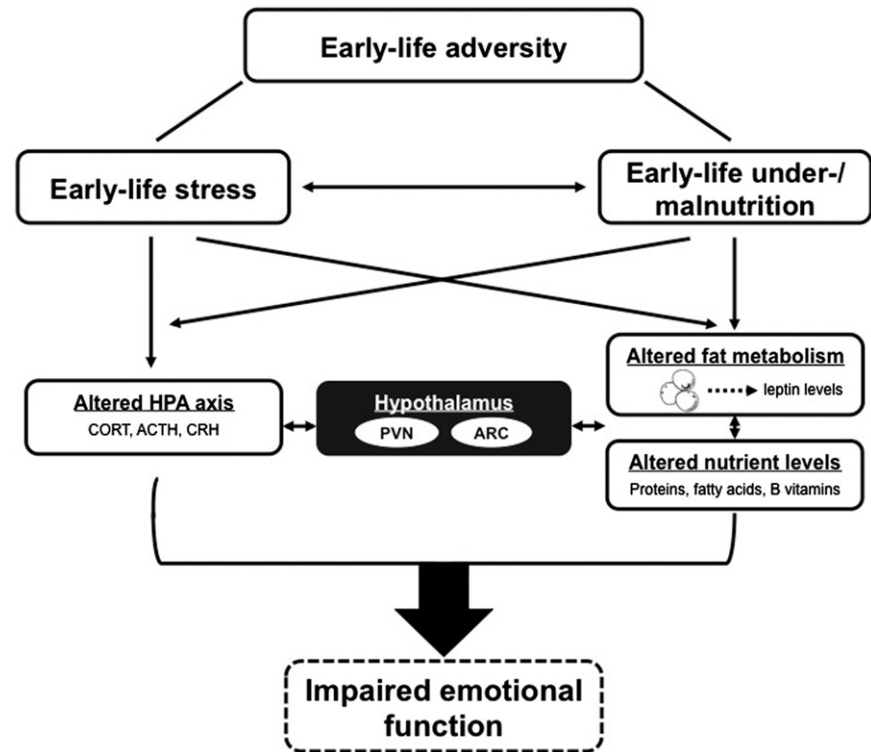
et al., 2009), poverty (Chugani et al., 2001) and maternal depression (Stevens et al., 2008), which are all accompanied by cognitive decline and an increased vulnerability to develop psychopathology later in life. However, the exact mechanisms underlying these programming effects are not fully understood. Important questions in this respect are: (1) which key elements in the early environment play a role? And: (2) what are the cellular and molecular mechanisms responsible for the lifelong programming of the brain?

The EL environment encompasses several elements, including sensory stimuli from the mother, neuroendocrine signals and nutrition (Baram et al., 2012; Joëls & Baram, 2009; Korosi & Baram, 2009; Lucassen et al., 2013). Alterations in either one or multiple of these elements will impact brain development during specific critical periods and thereby affect brain structure and function later in life. For example, (pre)clinical studies show that disruption in maternal care influence the development of emotional and cognitive functioning throughout life (Baram et al., 2012; Heim et al., 2008; Maselko et al., 2011; Tyrka et al., 2008). It is remarkable that also adverse nutrition-related changes early in life affect the stress system and pre-dispose an individual to

\*This article is based on work presented at the 5th Brain and Behavior: "Good Stress, Bad Stress and Very Bad Stress", February 2014.

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Figure 1. Schematic representation of the interaction of early-life stress and early-life nutrition in the programming of the HPA axis and emotional function by early-life adversity. This figure shows the complexity of the closely interrelated factors that are able to influence each other and contribute to the outcome of developing lasting effects on emotional behavior. However, to what extent alterations in the fat metabolism and nutrient levels play a role in the development of impaired emotional functions is not yet clear. ACTH, adrenocorticotropic hormone; ARC, arcuate nucleus; CORT, corticosterone; CRH, corticotropin-releasin hormone; HPA axis, hypothalamic–pituitary–adrenal axis; PVN, paraventricular nucleus.



emotional disturbances in adulthood as well (Brown et al., 2000; de Rooij et al., 2006; Heijmans et al., 2008; Painter et al., 2005). For example, exposure to famine in the Dutch Hunger Winter during the first trimester resulted in a 2-fold increase in the risk to develop schizophrenia, while exposure to famine in the second and third trimester is associated with an increased risk to develop affective psychosis (Brown & Susser, 2008; Brown et al., 1995; Hulshoff Pol et al., 2000). What is not yet clear is whether and how these seemingly uncoordinated sensory stimuli, the stress-induced hormonal changes and the nutritional environment interact, affect one another, and whether there might be a common pathway via which these inputs affect and program our brain (Figure 1).

Clearly, the early stressful environment is able to affect the nutritional status of the offspring and adverse nutritional environments can be considered as a stress condition. Stress and nutrition are indeed closely interrelated factors (Hoeijmakers et al., 2015; Lucassen et al., 2013; Spencer, 2013; Walker, 2010). An extreme clinical example that illustrates the close interplay between stress and nutrition is a pediatric condition named non-organic failure to thrive (NOFTT), the most frequent (up to 90%) form of failure to thrive (Cole & Lanham, 2011). NOFTT consists of a decelerated or arrested physical growth that involves a state of undernutrition due to inadequate caloric intake and absorption, which however develops without implications of major metabolic diseases and is directly caused by behavioral or psychosocial problems. In fact, postnatal factors, such as economic status and parental child abuse/neglect, are associated with NOFTT (Black et al., 1995; Cole & Lanham, 2011; Wright, 2006). Moreover, there is some evidence pointing towards a positive correlation between the severity of growth deficiency in children who experienced NOFTT and the development of cognitive, mental or emotional disturbances later in life (Corbett & Drewett, 2004;

Glaser et al., 1968; Muñoz-Hoyos et al., 2011), but see (Rudolf, 2005).

In this review, we will discuss the effects of ELS and under-/malnutrition on the developing brain with a focus on the programming of the neuroendocrine stress system and emotional function. We will examine in detail the evidence from clinical and pre-clinical studies on the effects of ELS and early-life nutrition on these systems and cover the specific role of stress, metabolic hormones, maternal sensory stimuli as well as nutrition and highlight their interaction in the lasting effects (Figure 1). Finally, we will address some of the epigenetic mechanisms that might mediate these alterations.

## Long-term consequences of early-life stress on emotional behavior and the neuroendocrine stress system

### Development of the neuroendocrine stress system

The neuroendocrine stress system is largely under control of the hypothalamus. Both physical and psychological stressors activate the hypothalamic–pituitary–adrenal (HPA) axis by rapidly triggering the release of the corticotropin-releasing hormone (CRH) from the paraventricular nucleus (PVN), which in turn causes the secretion of adrenocorticotropic hormone (ACTH) from the pituitary into the blood (de Kloet et al., 2005). ACTH stimulates the synthesis and secretion of glucocorticoids (GCs) from the adrenal cortex, i.e. corticosterone (CORT) and cortisol in rodents and humans, respectively. The HPA axis is under negative feedback control of GCs binding to glucocorticoid receptors (GRs) in the hypothalamus and pituitary gland, leading to the inhibition of CRH and ACTH release and causing tight regulation of the stress response system.

The development of this important hypothalamic circuit occurs until the first 2–3 postnatal weeks of a rodent life

(Morgane et al., 2002), while in humans it takes place throughout the entire gestation and is not completed until the last trimester (Bouret & Simerly, 2006; Koutcherov et al., 2003). The HPA axis of rodents in early postnatal life undergoes a period of reduced responsiveness (Pryce et al., 2002), termed the stress hypo-responsive period (SHRP), which is largely controlled by maternal care (Levine, 2001). The human equivalent to the rodent SHRP appears to take place at the end of the first year of life (Gunnar & Quevedo, 2007). The SHRP is characterized by an active suppression to secrete ACTH and CORT in response to various stressors. However, this suppression is dependent on the nature of the stressor, for example, specific age-appropriate stressors such as the absence of the mother, inadequate maternal care or cold exposure can still elicit an HPA axis activation during the SHRP (Avishai-Eliner et al., 1995; Dent et al., 2000). Consequently, manipulations that disturb the dam–pup relationship are very effective in inducing ELS conditions, particularly during the first 2 weeks of a rodent life when the pups depend on the dam for nutrition, warmth and sensory stimulation (see next section for more details).

In the next sections, we will consider how adverse experiences during the perinatal period can affect long-term HPA axis activity and emotional functions and present the evidence for the modulatory role of key elements (sensory stimuli, stress as well as metabolic hormones and nutrition) and their interaction during adverse EL experiences on the development and function of the neuroendocrine stress system and emotional behavior.

### **Lasting effects of early-life stress on the hypothalamic–pituitary–adrenal axis and emotional behavior**

Early-life stress is associated with an altered responsiveness of the HPA axis in adulthood. This has been established both in clinical as well as pre-clinical studies. Indeed, humans exposed to ELS have increased HPA axis reactivity in response to physiological and pharmacological stressors (Lupien et al., 2009; Pesonen et al., 2010; Teicher et al., 2012; Tyrka et al., 2008) as well as a higher incidence of developing cognitive and emotional impairments in adulthood (Abe et al., 2007; Bale et al., 2010; Glover, 2011; Gershon et al., 2013; Heim et al., 2008; Loman et al., 2010; Pesonen et al., 2007). Similarly, experimentally induced modulations of the EL environment in rodents affect several modulators of the neuroendocrine stress system on the long-term, e.g. through lasting changes in the expression of CRH and GR genes, which will be discussed in detail in this section (Avishai-Eliner et al., 2001; Brunson et al., 2001; Chen et al., 2010; Korosi & Baram, 2010; Rincón-Cortés & Sullivan, 2014). The effects of ELS on HPA axis activity and emotional function of the offspring have also been extensively studied in primate (Pryce et al., 2002), however, we will here review the studies based on rodent postnatal stress models (Naninck et al., 2015; Oomen et al., 2011; Workel et al., 2001) (Table 1).

Most postnatal stress models consist of disrupting the dam–pup interaction by a single prolonged separation for 24 h (maternal deprivation; MD) or by repeated daily separations

of the dam and pups for 3–8 h (maternal separation; MS). For example, following MD in rats at postnatal (P) day 5 or 8, basal expression of CRH mRNA in the PVN was reported to be either unchanged (Avishai-Eliner et al., 1995; Korosi et al., 2010) or reduced (Schmidt et al., 2004), accompanied by reduced CRH receptor 2 (CRFR<sub>2</sub>) mRNA expression in the ventromedial hypothalamus (Eghbal-Ahmadi et al., 1997). In addition, ACTH and CORT responses to a stressor, such as cold exposure or restraint, were markedly increased in pre-pubertal rats (Avishai-Eliner et al., 1995; Dent et al., 2000; Vázquez et al., 1996). Moreover, repeated periodic MD of 180 min from P3 to P10 in rats leads to later anxiety-related behavior that was accompanied with elevated ACTH response after elevated plus maze exposure (Wigger & Neumann, 1999). Changes in HPA axis activity in response to stress are still present in adulthood, but the direction of the effect largely depends on the age of the animal and on the testing conditions (Workel et al., 2001).

Similarly, repeated daily MS in rats for several hours during the first 2 postnatal weeks augments the hormonal stress response in rodents throughout life and is accompanied by decreased GR binding in both hippocampus and hypothalamus (Chen et al., 2012; Ladd et al., 2000) but see (Lehmann et al., 2002; Pryce et al., 2001), associated with increased fearfulness in tests of novelty and anxiety (Caldji et al., 1998; de Kloet et al., 2005; Huot et al., 2001; Ladd et al., 2004; Romeo et al., 2003; Wigger & Neumann, 1999) and depressive-like behavior at an adult age (Huot et al., 2002; Ladd et al., 2000).

Interestingly, also the expression level of several genes that are essential regulators of the stress response are persistently altered in repeatedly separated rats. This includes for example increased CRH expression in the amygdala, locus coeruleus (LC) and parabrachial nucleus, increased stress-induced CRH hnRNA expression in the PVN (Chen et al., 2012) and increased CRH receptor 1 (CRFR<sub>1</sub>) mRNA expression levels in the LC and raphe nucleus (Ladd et al., 1996; Pryce et al., 2002). Furthermore, levels of arginine vasopressin (AVP) in the PVN and bed nucleus of the stria terminalis (BnST) have been reported to be either increased (Levine, 2001; Veenema & Neumann, 2009) or decreased by MS (Desbonnet et al., 2008; Gunnar & Quevedo, 2007). This discrepancy in AVP level changes are possibly caused by sex specific effects (Desbonnet et al., 2008).

Next to artificial modulation of dam–pup interaction, natural variations in maternal care combined with selected breeding programs have been widely used to study the effects of differential maternal care on the HPA axis. Low amounts of Licking and Grooming (LG) in rats lead to increased ACTH and CORT release in response to stress in adulthood as well as lasting increased hypothalamic CRH expression and reduced hippocampal GR expression (Liu, 1997; Weaver et al., 2004). On the emotional level, low LG increases anxiety-like behavior in rats (Caldji et al., 1998).

So far, we have described how MS/MD and natural variation in maternal care affect the HPA axis and emotional function later in life. However, these models all involve acute or recurrent stress, and as such lack some important aspects of ELS present in humans, in which stress is typically chronic and the mother/caregiver is present but unable to

Table 1. Examples of early-life interventions affecting emotional behavior and the neuroendocrine system.

Early-life manipulation	Effects on HPA axis	Effects on metabolism	Epigenetic alterations	Anxiety- or depressive-like behavior in adulthood	Species	References
<b>Early-life stress</b> Low maternal care	↓GR (hippocampus; P90) <sup>1</sup> ↓CRH (hypothalamus; P100) <sup>2</sup> ↑CORT and ACTH (stress-induced; P100) <sup>2</sup>	?	↑DNA methylation of GR promoter (hippocampus; P90) <sup>1</sup>	↑ <sup>3</sup>	Rats	1. Weaver et al. (2004) 2. Liu (1997) 3. Caldji et al. (1998)
Handling	↑GR (hippocampus; P120) <sup>4</sup> ↓CRH (hypothalamus; P9) <sup>5</sup> ↓CORT and ACTH (stress-induced; P23) <sup>6</sup>	?	↑NRSF expression (hypothalamus; P9–P45) <sup>5</sup>	↓ <sup>7</sup>	Rats	4. Meaney et al. (1985) 5. Korosi et al. (2010) 6. Fenoglio et al. (2006) 7. Francis & Meaney (1999)
Maternal separation	↓GR (hippocampus; P124) <sup>8*</sup> ↑CRH (hypothalamus; P60) <sup>9*</sup> ↑CORT and ACTH (stress-induced; P115) <sup>8*</sup>	↓Plasma glucose and leptin levels (P8) <sup>10#</sup> ↑Plasma ghrelin levels (P8) <sup>10#</sup>	↓DNA methylation of CRH promoter (hypothalamus; P60) <sup>9*</sup> ↓HDAC expression (forebrain neocortex; P35) <sup>11#</sup> ↑H4K12ac (forebrain neocortex; P60) <sup>11#</sup>	↑ <sup>12#</sup>	Rats*/Mice <sup>#</sup>	8. Ladd et al. (2004) 9. Chen et al. (2012) 10. Schmidt et al. (2006) 11. Levine et al. (2012) 12. Romeo et al. (2003)
Maternal deprivation	↓GR (hippocampus; P9, P12) <sup>13</sup> =CRH (hypothalamus; P9) <sup>14</sup> ↑CORT (basal and stress-induced; P9 and P12) <sup>13</sup> ↑ACTH (stress-induced; P9 and P12) <sup>13</sup>	↓Plasma leptin levels (P75) <sup>15</sup>	?	↑ <sup>16</sup>	Rats	13. Vazquez et al. (1996) 14. Avishai-Eliner et al. (1995) 15. Viveros et al. (2010) 16. Wigger & Neumann (1999)
Childhood trauma (abuse/maltreatment)	↓GR (hippocampus; 20–40 years of age) <sup>17</sup>	Blunted elevation in leptin levels (12 years of age) <sup>18</sup>	↑Cytosine methylation of NR3C1 promoter (20–40 years of age) <sup>17</sup> ↓DNA methylation capacity by C677T polymorphism in MTHFR gene (18–63 years of age) <sup>19</sup>	↑Risk to develop depression <sup>19,20</sup>	Humans	17. McGowan et al. (2009) 18. Danese et al. (2014) 19. Lok et al. (2013) 20. Heim et al. (2008)

(continued)

Table 1. Continued

Early-life manipulation	Effects on HPA axis	Effects on metabolism	Epigenetic alterations	Anxiety- or depressive-like behavior in adulthood	Species	References
<b>Early-life nutrition</b> 50% food restriction	↑MR and GR (hippocampus; P21) <sup>21</sup> =CRH (hypothalamus; P21) <sup>21</sup> =CORT and ↓ACTH (basal, P21) <sup>21</sup> ↑GR (hippocampus; 4 weeks) <sup>25</sup> =CORT and ↓ACTH (basal; 4 weeks) <sup>25</sup>	↓Amount of fat depots (P21) <sup>22</sup> ↓Plasma leptin levels (P21) <sup>22</sup>	↑Homocysteine (serum; P4) <sup>23</sup>	↑ <sup>24</sup>	Rats	21. Vieau et al. (2007) 22. Leonhardt et al. (2003) 23. Petrie et al. (2007) 24. Jahng et al. (2007)
Early protein malnutrition (protein restriction/low protein)	↑GR (hippocampus; P8 and P14) <sup>27</sup> ↓CRH (hypothalamus; P8 and P14) <sup>27</sup> ↑CORT and ACTH (basal; P14 and P21) <sup>27</sup> ↑ACTH (stress-induced; > P21) <sup>30*</sup>	↓GR (liver; P34) <sup>25</sup> ↑GR and 11β-HSD1 (fat tissue; P21) <sup>27</sup> ↑Plasma leptin and FFA levels (P8–P120) <sup>27</sup>	↓DNA methylation of GR10 promoter (liver; P34) <sup>25</sup> ↑Methylation of POMC promoter (hypothalamus; P21) <sup>28</sup>	↑ <sup>26</sup> ↓ <sup>29</sup>	Rats	25. Lillycrop et al. (2007) 26. Belluscio et al. (2014) 27. Boullu-Ciocca et al. (2005) 28. Plagemann et al. (2009) 29. Spencer & Tilbrook (2009)
Small litter size (postnatal overfeeding)	↑CORT and ACTH (basal; P14 and P21) <sup>27</sup> ↑ACTH (stress-induced; > P21) <sup>30*</sup>	↓Plasma leptin levels (>P21) <sup>30*</sup>	↑Methylation of leptin promoter (adipocytes; 11 weeks) <sup>31*</sup>	↑ <sup>32#,33*</sup>	Rats*/Mice <sup>#</sup>	30. Trotter et al. (1998) 31. Milagro et al. (2009) 32. Peleg-Raibstein et al. (2012) 33. Giriko et al. (2013) 34. Chen & Su (2013) 35. Jen et al. (2009) 36. He et al. (2014)
High fat diet	↑CORT (stress-induced; 10 weeks) <sup>34*</sup>	↓Bodyweight (P150) <sup>35*</sup> ↑Omega-6 (milk; P14) <sup>35*</sup> ↑Amount of abdominal fat (P140) <sup>37</sup> ↑Plasma leptin and insulin levels (P140) <sup>37</sup> ↓Fatty acid synthesis (maternal liver; P21) <sup>40</sup> ?	↓MeCP2 DNA methylation (whole brain, P19) <sup>36#</sup>	↑ <sup>34*</sup>	Rats*/Mice <sup>#</sup>	37. Bernardi et al. (2013) 38. Mathieu et al. (2008) 39. Mathieu et al. (2011)
Maternal separation+ omega-3 deficiency	?	?	?	↑ <sup>38,39</sup>	Rats	40. McNeil et al. (2008) 41. Konycheva et al. (2011)
Methyl donor deficiency	?	?	=Methylation of GR and 11β-HSD2 (hippocampus; P110) <sup>41</sup> ↑DNA methylation of CRH and NR3C1 promoters (placenta) <sup>42S</sup>	↑ <sup>41</sup> ↓ <sup>43*</sup>	Rats	42. Jiang et al. (2012) 43. Schulz et al. (2014)
High choline	↓CRH (placenta) <sup>42S</sup> ↓Cortisol (cord plasma) <sup>42S</sup>	?			Rats*/Humans <sup>S</sup>	
Famine	=Cortisol (baseline; 48–53 years of age) <sup>44</sup>	↑LDL/HDL ratio (blood; 48–53 years of age) <sup>45</sup>	↓DNA methylation of IGF2 gene (blood; 50–60 years of age) <sup>46</sup>	↑Risk of developing major affective disorder <sup>47</sup>	Humans	44. de Rooij et al. (2006) 45. Painter et al. (2005) 46. Heijmans et al. (2008) 47. Brown et al. (2000)

\*Rats, #Mice, \$Humans.

11β-HSD1, 11β-hydroxysteroid dehydrogenase 1; ACTH, adrenocorticotropic hormone; CORT, corticosterone; CRH, corticotropin-releasing hormone; DNA, deoxyribonucleic acid; FFA, free fatty acid; GR, glucocorticoid receptor; H4K12ac, histone H4 lysine 12 acetylation; HDAC, histone deacetylase; MeCP2, methyl CpG-binding protein 2; MTHFR, 5,10-methylene tetrahydrofolate reductase; NR3C1, nuclear receptor subfamily 3, group C, member 1 (alias GR); NRSF, neuron restrictive silencing factor; P, postnatal; POMC, proopiomelanocortin.

give her child the appropriate care (Gaudin et al., 1996; Kendall-Tackett, 2007; Koenen et al., 2003). Therefore, an animal model of actual *chronic* ELS was developed to recapitulate important elements of the human EL adverse condition (Avishai-Eliner et al., 2001; Baram et al., 2012; Ivy et al., 2008; Liao et al., 2014; Rice et al., 2008; Rincón-Cortés & Sullivan, 2014; Wang et al., 2013). In this model, the amount of nesting and bedding material is limited during the first postnatal week, inducing chronic stress in the dam which results in erratic, fragmented maternal care (i.e. shortened bouts of nurturing behavior and frequent shifts between behaviors). The fragmentation of maternal care subsequently causes chronic ELS in the pups, as is evident from their elevated basal plasma CORT levels, a transient reduction in weight gain and increased adrenal weight by the end of the 1-week stress period at P9. These physiological changes at P9 are accompanied by reduced CRH receptor binding in the pituitary, reduced in CRH and GR mRNA expression in the PVN and reduced CRFR<sub>1</sub> expression in the hippocampus as well as GR expression in the frontal cortex, while hypothalamic AVP levels are unaffected (Avishai-Eliner et al., 2001; Gilles et al., 1996). While the ELS-induced reduction in hypothalamic CRH was found to be transient in rats (Avishai-Eliner et al., 2001), it was still present in adult mice (Rice et al., 2008).

These above-summarized studies clearly highlight the importance of maternal presence and the quality and quantity of her care that appear to define the development and later life function of the neuroendocrine stress system and emotional function. Mother-offspring interaction clearly encompasses multiple elements including sensory stimuli, but also nutrition. The importance of maternal tactile stimulation is clearly highlighted in the above-reviewed studies. However, interestingly, there is some evidence supporting rather a synergistic effect of tactile stimulation and nutrition. For example, stroking the rat pups to mimic maternal tactile stimulation prevented several effects of early stress, including on metabolic derangements (Haley et al., 2013; Moyer-Mileur et al., 2011; van Oers et al., 1999). Remarkably, the adverse effects of MD on HPA axis function in rats were reversible only when combining stroking with food administration (van Oers et al., 1999). This highlights the possible critical involvement of the nutritional element as well, next to the well-investigated roles of sensory stimuli, stress related hormones and neuropeptides in mediating the above-described effects. The role of the nutritional element in this context, however, has been largely ignored. In the next section, we review the available information on the role of EL nutrition in regulating the stress system and emotional functions.

### **Long-term consequences of perinatal nutrition on emotional behavior and the neuroendocrine stress system**

Nutritional deficiency, i.e. under- and malnutrition during critical developmental periods leads to permanent effects on the susceptibility of an individual to develop psychopathology later in life (Langley-Evans, 2009; Prado & Dewey, 2014). Undernutrition is defined as a state of chronic inadequate (amount of) nutrition, with all the required nutrients present in

the diet. In contrast, malnutrition is the lack of one or more essential nutrients from the diet (Benton, 2010). Both perinatal under- and malnutrition increase the vulnerability to develop psychiatric disorders, e.g. schizophrenia and depression (Brown et al., 2000; Lesage et al., 2006). Considering the extraordinary need for nutrients during early development, it is not surprising that any sort of deficiency in this realm during these sensitive developmental periods might lastingly affect emotional functions later in life or for example on the hypothalamic circuits development (Table 1).

One way to model under- or over-nutrition is by modulating litter size. For instance, reducing the litter sizes of rats to three or four pups leads to higher body fat mass and metabolic deregulations in adulthood compared to normal litter sizes (Morris et al., 2005). These changes in small litter-raised rats are accompanied by long-term alterations in emotional functions as demonstrated by reduced anxious behavior when compared to rats raised in large litter sizes (Spencer & Tilbrook, 2009). This behavioral phenotype is accompanied by faster HPA axis maturation early in life, which was evidenced by increased basal levels of circulating ACTH and CORT at P14 and P21. Also, the decrease of CRH and increase of GR mRNA expressions levels in hypothalamic PVN was accelerated at P8 and P14 in rats (Boullu-Ciocca et al., 2005). Furthermore, rats that underwent the small litter size model exhibited increased amounts of neuronal activation (c-FOS expression) of the CRH expressing PVN neurons in response to restraint stress (Dayas et al., 1999; Spencer & Tilbrook, 2009). On the metabolic level, small litter-raised rats showed higher GR and 11 $\beta$ -HSD1 expression in fat tissue, accompanied by increased circulating leptin levels (Boullu-Ciocca et al., 2005). These changes are possibly explained by the fact that the reduction in litter size led to an increase of 20–30% in milk consumption. To what extent this manipulation affects maternal care was uninvestigated. In contrast, rats raised in large litters consumed less maternal milk, exhibited slower growth, were associated with reduced stress-induced HPA axis responses and returned faster to baseline levels (Spencer, 2013).

Several other animal models have been used to study how alterations in the early nutritional environment affect the stress system and emotional functions. The most widely studied ones are 50% food restriction (FR50), high fat diet (HF) and maternal protein restriction (PR) during gestation, lactation or both. Rat offspring of mothers that underwent FR50 are characterized by increased depressive-like and anxious behavior at P28 (Jahng et al., 2007), increased hippocampal MR and GR gene expression, accompanied by decreased ACTH plasma levels at weaning period and without alterations in basal CORT or CRH (Leonhardt et al., 2002; Vieau et al., 2007). In adulthood, the increase in hippocampal GR mRNA expression, but not MR, returns to control levels (Sebaai et al., 2004). In addition to the effects on emotion and neuroendocrine stress system, rat offspring raised by mothers exposed to FR50 during the perinatal period were also affected metabolically. This was evidenced by growth retardation in offspring, reduced amounts of different fat depots and reduced circulating leptin levels at weaning (Leonhardt et al., 2003). In addition, exposure to prenatal maternal undernutrition followed by postnatal HF diet in rats

resulted in increased expression of orexigenic genes, causing a net result of increased appetite (Ikenasio-Thorpe et al., 2007).

These examples clearly show the close relationship between alterations in nutrition, metabolism and the development of long-term regulation of the HPA axis and emotional function (Figure 1). However, how do these changes modulate one another? In the following sections, we will discuss in detail the role of metabolic hormones as well as the effects of the lack or excess of specific nutrients on the neuroendocrine stress system.

### Role of metabolic hormones in regulating the hypothalamic–pituitary–adrenal axis and brain function

A key hormone in regulating processes associated with the hypothalamic feeding circuitry and the neuroendocrine system is the anorexigenic hormone leptin (Morrison, 2009). Leptin release from fat cells causes a loss of appetite and enhances energy expenditure via its actions in the arcuate nucleus of the hypothalamus (ARH) (Mainardi et al., 2013; Morton et al., 2006). Importantly, levels of leptin during the sensitive period of brain development are of utmost importance. In fact, there is a leptin surge occurring between P4 and P16 in rodents that is necessary to form proper connectivity within the hypothalamic circuitry. The absence of the leptin surge in mice during this specific developmental period leads to lasting alterations in feeding behavior and stress responses (Ahima et al., 1998; Granado et al., 2012), and leptin injections within this period in mice affect the development of neural ARH projections (Bouret et al., 2004). Indeed, advancing the time of onset of this leptin surge at P2 in rats results in a decrease of food intake and ablating the surge at P9 leads to reduced body weight and fat mass in adulthood (Granado et al., 2011). There is evidence that this leptin surge is not only crucial for the ARH-feeding circuit development, but also for correct development and function of the neuroendocrine system. Indeed, chronic leptin treatment early in life in rats leads to lifelong altered stress-induced HPA axis activity, accompanied by reduced PVN-CRF expression and increased GR expression in the hippocampus and PVN (Oates et al., 2000; Proulx et al., 2001). The fact that the nutrition-related metabolic hormone leptin can act on the stress system is not surprising considering the high expression of leptin receptors in brain areas related to stress, such as the hypothalamus and hippocampus (Li et al., 2002; Scott et al., 2009).

Based on the evidence presented above, it appears that ELS and EL malnutrition lastingly program the neuroendocrine stress system. In fact, the two main hypothalamic nuclei, PVN and ARH, involved in regulating the neuroendocrine stress system and the metabolism as well as feeding behavior, respectively, are neuroanatomical strikingly close (Bouret et al., 2004). In addition, there is increasing evidence (presented above) that the metabolic hormone leptin is able to affect and program these systems as well. These evidence altogether strongly points towards an intense cross-talk between these two systems. Thus, an important question that arises is whether ELS-induced changes in metabolic

hormones might possibly play a role in the programming of the stress system. This could be viewed in two ways: (1) ELS induced alterations in HPA axis activity might trigger metabolic changes, resulting in changes in peripheral metabolic hormones, which could then be involved in reshaping the hypothalamic feeding and/or stress circuitries and/or (2) ELS might result in undernutrition or decreased caloric intake, which in turn results in reducing circulating leptin levels that could then reshape HPA axis responses to stress. Based on the current knowledge, we are unable to clarify the order of causality and clearly more research in this area is needed. However, there is some evidence that metabolic hormones might play a role in programming the neuroendocrine system and/or hypothalamic circuits.

Indeed, stress-related hormones are able to affect the functioning of metabolic hormones (Joung et al., 2014) and MS on P8 from 4 to 12 h in mice leads to reductions of circulating glucose as well as leptin levels and increases in ghrelin levels early in life (Schmidt et al., 2006). Further pointing to a key modulating role of these metabolic hormones in the programming of the HPA axis; blocking the MS-induced ghrelin increase could reverse the MS effects on the HPA axis as well. Long-term effects were not presented in this study, however, MD in rats leads to long-term reductions in leptin levels at the age of P75 (Viveros et al., 2010). How exactly glucocorticoid and metabolic hormones interact is not resolved, but importantly glucocorticoids play a pivotal role in regulating lipid homeostasis and are one of the most potent stimulators of leptin expression in white adipose tissues (Bradley & Cheatham, 1999; Havel, 2004).

How exactly are these changes in metabolic mediators involved in the programming of the stress system? One possibility is that the ELS-induced reduction in leptin interferes with the leptin surge (see above) and may thereby possibly influence the proper developmental trajectory of the hypothalamus (Bouret & Simerly, 2006; Bouret et al., 2004), ultimately affecting neuroendocrine and eating behavior regulating centers. However, further testing of this possibility is required.

So far, we have discussed the effects of stress and metabolic factors on the neuroendocrine stress system and emotional function. However, next to stress and metabolic hormones, ELS and malnutrition clearly affect specific nutrient intake/availability. Considering the enormous demand for nutrients in the EL period, nutrition might play a crucial role in the lasting effects induced by EL adversities. In the next section, we will discuss the role of (the lack of) specific macro- and micronutrients on the development and function of the neuroendocrine stress system and emotional function.

### Nutrients and the stress system

There are several key nutrients that are extremely important during development including among others, not only proteins, fatty acids, choline but also essential micronutrients such as B vitamins and essential amino acids, e.g. methionine (Benton, 2011; van de Rest et al., 2012; Walker, 2005). The information on how the availability of these nutrients affects brain development, in particular how it programs the hypothalamic



system, has been addressed only to some extent and is fragmented, indicating the need for more detailed research in this context. We will here discuss the described effects of imbalanced perinatal protein and fat on HPA axis programming.

#### *Lifelong effects of perinatal low protein diet on the hypothalamic–pituitary–adrenal axis and emotional function*

The importance of protein intake early in life has been largely studied using maternal protein restriction (PR) during gestation and/or lactation. Maternal PR in rats induces a blunted diurnal pattern of ACTH plasma concentrations, elevated GR expression in the hippocampus and no changes in basal CORT (Langley-Evans et al., 1996). In addition, perinatal PR in rat dams has been associated with alterations of adhesion molecules in the vascular endothelium of the placenta as well as reduced expression levels of placental 11 $\beta$ -hydroxysteroid dehydrogenase 2 (11 $\beta$ -HSD2) (Langley-Evans, 2009; Langley-Evans et al., 1996), resulting in higher placental permeability. Since 11 $\beta$ -HSD2 enzymes convert active GCs into inactive forms (Edwards et al., 1996; Seckl et al., 2000), this reduction could lead to high GC exposure from the maternal compartment to fetal tissues. As a result, these high GC levels might lead to, among others, disrupted HPA axis development and a higher CORT response upon encountering stress in adulthood (Lesage et al., 2006). Interestingly, on the level of emotional functions, offspring mice of dams that were protein-malnourished show increased anxious and depressive-like behavior (Belluscio et al., 2014). Altogether, these examples indicate that alterations in protein availability early in life can program the HPA axis and might therefore play a role in increasing the risk to develop stress-related disorders later in life.

#### *Effects of fat on the hypothalamic–pituitary–adrenal axis and emotional behavior*

The potential of fatty acids to affect the HPA axis depends on the type of fat. Fatty acids can be divided into four classes: saturated, *trans*, polyunsaturated and monounsaturated (Morris, 2011). The polyunsaturated type of fatty acids are essential for, among others, molecular signaling, synaptogenesis, energy storage as well as for membrane functions and are entirely obtained from the diet (Rapoport et al., 2007). Particularly unsaturated, and not saturated fatty acids, stimulate steroidogenesis in adrenocortical cells *in vitro* (Sarel & Widmaier, 1995). In addition, the synthesis of corticosteroids requires cholesterol from fat, which needs to be obtained via the diet, indicating that fatty acids potentially could have a strong influence on the HPA axis. Polyunsaturated fatty acids (PUFAs) are further divided into omega-3 fatty acids termed  $\alpha$ -linolenic acid (ALA), eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). DHA is the most abundant type of PUFAs in the central nervous system and, importantly, is indispensable for cell membrane building as well as proper functioning of the brain (Innis, 2008). PUFAs are also pivotal components in maternal milk, further supporting their importance for critical developmental processes during EL (Innis, 2014; Nishimura et al., 2014).

Depletion of omega-3 fatty acids and HF diets perinatally has been the two main experimental manipulations to explore

the effects of fats on brain development and (partly) to study its effects on HPA axis functioning and emotional function. Reducing omega-3 fatty acid in the diet for two generations in rats has been shown to reduce DHA levels in several brain regions, including the cerebellum, medulla, hypothalamus, striatum, hippocampus, cortex and midbrain (Xiao et al., 2006), suggesting that levels of fatty acid content of the brain can be manipulated through diet.

Docosahexaenoic acid (DHA) deficiency in rats during the pre-weaning, but not post-weaning period, resulted in lasting increased responsiveness of the HPA axis to stress, as indicated by increased and prolonged stress-induced CORT levels and heart rate changes in adulthood. This was accompanied by enhanced anxiety- and depressive-like behavior after forced swim test and elevated plus-maze, respectively (Chen & Su, 2013). Moreover, omega-3 PUFA deficiency in mice after weaning disrupts the GR mediated signaling pathway and causes HPA axis hyperactivity as shown by elevated plasma CORT levels at 3 months of age (Larrieu et al., 2014). Interestingly, depressive-like behavior induced by prenatal stress in rats could be reduced by omega-3 treatment during pregnancy and lactation (Borsonelo et al., 2011). The tight interaction between nutrition and stress is further highlighted by studies showing that rats exposed to omega-3 PUFA-deficient diet early in life and MS, were more anxious and fearful in inescapable situations compared to the ones that were exposed to MS alone (Mathieu et al., 2008, 2011). In addition, rats that underwent MS and omega-3 deficient diet exhibited metabolic alterations, such as increased abdominal fat, circulating leptin and insulin levels and increased sucrose consumption when compared to unhandled control animals that obtained sufficient omega-3 in their diet (Bernardi et al., 2013; Mathieu et al., 2008).

Interestingly, next to depletion of omega-3 fatty acid, increasing the amount of fats in general by HF diets early in life has lasting effects on the HPA axis, metabolism and emotional functions of the offspring as well. Indeed, HF feeding of rat dams during lactation led to increased fatty acids levels in maternal milk (Trottier et al., 1998). This in turn led to reductions in HPA axis responsiveness in the rat offspring up to the age of P21, as evidenced by diminished ACTH and faster recovery to baseline CORT levels in response to stress, and showed increased levels of leptin. After weaning, rat pups from the HF mothers had lower plasma leptin levels and increased stress-induced ACTH secretion. The inverse relationship between circulating leptin levels and HPA responses in pups creates the possibility that the effects of the HF diet on stress responsiveness are mediated by changes in leptin exposure during development (Trottier et al., 1998). Concerning the emotional behavior, mice offspring of dams fed a HF diet for 9 weeks (prior to gestation, gestation and lactation) showed higher anxiety-like behavior in adulthood (Peleg-Raibstein et al., 2012). In line with these findings on emotional behavior, early maternal exposure to HF diet in rats leads to an increased susceptibility to depressive behavior (Giriko et al., 2013).

Taken together, both stress and nutrition play profound roles during the early perinatal period, causing alterations in activity and sensitivity of the HPA axis, and thus modifying the vulnerability to develop psychopathologies later in life.

Importantly, as highlighted above, not only do these adversities often occur simultaneously, they are often interrelated, thereby indicating the need to consider these elements as acting synergistically rather than independently. Most likely, common mechanistic pathways underlie the effects of stress and nutritional stimuli, possibly involving epigenetic mechanisms. The next section will be devoted to discuss the role of epigenetic mechanisms in the lasting effects of ELS and EL nutrition and how specific nutrients might modulate the epigenome.

## Epigenetic mechanisms underlying the lasting effects of early-life experiences

### Effects of ELS on the epigenome

Over the past few years, a growing body of epidemiological as well as pre-clinical studies has demonstrated the role of epigenetic mechanisms in determining the lasting effects of EL experiences (Vaiserman, 2015). Epigenetics is a phenomenon that alters gene expression without eliciting changes in DNA sequence. Epigenetic modifications encompass among others DNA methylations, post-translational histone modifications and transcriptional non-coding RNA regulations. These modifications occur through alterations in the structure of the chromatin or the DNA, leading to the expression or repression of gene transcription, which is determined by the state of chromatin compaction: an open chromatin structure is transcriptionally active (euchromatin), whereas a condensed chromatin with tightly coiled DNA is associated with a transcriptional inactive state (heterochromatin). In general, DNA methylation predominantly leads to gene silencing, whereas histone acetylation usually promotes transcription. In mammals, DNA methylation occurs at cytosines through the effects of methyl-binding proteins (MeCP1, MeCP2, MBD1, MBD2, MBD3 and MBD4) and methylated CpG islands in the promoter region of genes repress gene expression by preventing transcription factors to bind at the promoter region. In addition, silencing via MeCP2 occurs partly by recruiting histone deacetylase (HDAC) activity, resulting in chromatin remodeling (Fuks et al., 2003).

Lasting effects of ELS on gene expression in the offspring are associated with epigenetic alterations. Indeed, ELS in mice induces DNA hypomethylation at the AVP gene, resulting in increased levels of AVP levels (Murgatroyd et al., 2009). Also, EL adversity from P1 to P7 by stress-abusive rat dams results in reduced brain-derived neurotrophic factor (BDNF) expression due to increased methylation at the BDNF exon IV promoter in the prefrontal cortex later in life (Roth et al., 2009). Differences in the amount of maternal care are also able to cause lasting modifications in DNA methylation and chromatin structure. For example, low-LG rat offspring show reduced GR gene expression in the hippocampus that is related to increased DNA methylation in exon 1<sub>7</sub> GR promoter at the region around the nerve growth factor inducible factor A (NGFIA) consensus sequence, resulting in increased histone acetylation of the GR (Weaver et al., 2004). Intriguingly, this programming is reversible by cross-fostering offspring of low-LG to high-LG mothers, which leads to hypomethylation of cytosines at the 5' CpG dinucleotide of the NGFIA consensus sequence (Weaver et al., 2004).

Accordingly, in the case of handling, where pups are separated daily from the mother for 15 min on P2 for at least 1 week or up to 3 weeks (Fenoglio et al., 2006; Francis & Meaney, 1999; Meaney et al., 1985), the changes induced by reductions in CRH expression levels are maintained by epigenetic mechanisms (Chen et al., 2012). Reduction in CRH levels in rats are accompanied with permanent increased levels of the neuron restrictive silencing factor [NRSF; also designated as repressor element 1-silencing transcription factor (REST)] (Korosi et al., 2010), which is a transcriptional repressor that has a binding site within the CRH gene (Seth & Majzoub, 2001) and concomitantly recruits the epigenetic machinery by driving histone deacetylation (Roopra et al., 2000). The short lack of maternal care during handling is not associated with deleterious effects, leading to a significantly higher amount of maternal sensory stimulation, such as LG towards the offspring after reunion.

In addition to these epigenetic changes on specific genes induced by these various EL experiences, there is evidence that these effects are affecting the epigenome more globally (Levine et al., 2012; McGowan et al., 2011).

### Effects of early-life nutrition on the epigenome

As in the case of stress, the effects of early nutrition might also be mediated by modulation of the epigenome (He et al., 2014; McNeil et al., 2008). This has mostly been addressed in the context of metabolic programming, which is in contrast to the scarce evidence of epigenetic effects of early nutritional manipulations in the brain. For example, changes in the methylation of the hypothalamic proopiomelanocortin (POMC) promoter have been found in rat pups that were allocated to small litter sizes (Plagemann et al., 2009). Furthermore, in both rats and mice, administering a FR50 diet to pregnant rodents resulted in elevated homocysteine concentrations in the earliest stages of gestation (Petrie et al., 2007). In rats, HF resulted in high methylation of the leptin promoter in adipocytes (Milagro et al., 2009). On the other hand, maternal PR diet leads to reduced expression of DNA (cytosine-5)-methyltransferase 1 and 2 (Dnmt1) and increased hypomethylation of the GR1<sub>10</sub> promoter, which in turn caused increases in GR expression (Lillycrop et al., 2007). Interestingly, maternal supplementation with folic acid counteracted this reduced expression of Dnmt1 enzymes (James et al., 2002).

Another possible epigenetic process that could be important in mediating the lasting effects of ELS and EL malnutrition is histone acetylation. ELS and EL malnutrition has been shown to affect acetylation of histones (Burdge et al., 2007; Levine et al., 2012; Portha et al., 2014; Xie et al., 2013). In fact, fatty acids are potential donors of acetyl groups (Burdge & Lillycrop, 2014). As discussed in the previous sections, ELS might lead to alterations in fat metabolism (Danese et al., 2014; Schmidt et al., 2006; Viveros et al., 2010) and thereby altering circulating and available fatty acids. Moreover, manipulations of fat contents early in life have been shown to affect HPA axis functioning as well (Chen & Su, 2013; Larrieu et al., 2014; Trottier et al., 1998). Therefore, in future research, it will be important to consider acetylation as a possible mechanism in mediating these effects.

The following sub-section will highlight the possible importance of a selection of B-vitamins, such as vitamin B6, B9 (folate), B12 (cobalamin) as well as methionine and choline in mediating the lasting effects of ELS and EL malnutrition. These micronutrients play a crucial role in neuronal cell growth and development during the perinatal period and are also key co-factors and metabolites of the one-carbon (1C) metabolism. These 1C metabolites (referred further in the text as methyl donors) are required for methylation of DNA and histones and therefore associated to the epigenetic machinery.

Even though it is not known yet how the (lack of) these 1C metabolites early in life might specifically program HPA axis and emotional function, we will discuss the possibilities that it might involve the modulation of the epigenetic modifications and/or DNA synthesis as well as DNA repair processes.

#### *Effects of dietary methyl donor nutrients on the brain and the epigenetic machinery*

Vitamin B6, B9 [folate and its active form 5-methyl-tetrahydrofolate (5-MTHF)] and B12 (cobalamin) belong to the family of B vitamins and in addition to their role as suppliers of methyl donors, deficits of these micronutrients can lead to cognitive impairments and anxiety. Indeed, male weanling mice receiving diets deficient in B vitamins for 10 weeks displayed impaired spatial learning and memory (Troen et al., 2008). Furthermore, rats exposed to prenatal vitamin B6 deficient diets displayed functional and structural impairments in the hippocampus (Krishna & Ramakrishna, 2004). On the emotional level, dietary methyl donor deficiency in rats during pregnancy leads to lasting increased anxiety levels, without changes in GR or 11 $\beta$ -HSD2 methylation in the hippocampus (Konycheva et al., 2011). The brain can additionally be affected by pyridoxal phosphate (PLP), the active coenzyme of vitamin B6. It influences brain development due to its role in the synthesis of nucleic acids as well as playing a role in the 1C metabolism by producing 5,10-methylene tetrahydrofolate (5,10-CH<sub>2</sub>-THF) from THF. Interestingly, vitamin B6 also modulates the HPA axis by regulating multiple members of the steroid hormone receptor family, among others, the GR (Allgood et al., 1990; Oka, 2001). These studies clearly indicate the need to gain further knowledge on how these nutrients might regulate hypothalamic development and function as well.

Folate (vitamin B9) plays a major role throughout life and is involved in brain development. Folate is a well-known nutrient due to its crucial role in the first trimester of pregnancy where its inadequacy leads to congenital neural tube defects (Morris, 2011). In addition, folate plays important roles in the metabolism of DNA and erythrocytes as well as the synthesis of methionine and S-adenosylmethionine (SAM). The activation of methionine to SAM ensues using the folate-derived methyl groups in numerous DNA methylation reactions. The rate-limiting enzyme in the methylation cycle named 5,10-methylene tetrahydrofolate reductase (MTHFR), converts 5,10-methylene THF to 5-MTHF. Interestingly, in humans, the specific C677T single-nucleotide polymorphism in the MTHFR gene is accompanied with decreased DNA methylation capacity and increased oxidative

stress, which aggravates the outcome on developing major depressive disorder in adulthood when traumatic childhood was encountered early in life (Lok et al., 2013). The importance of folate is further demonstrated in humans by the association of low maternal folate status during early pregnancy and emotional problems in the offspring later in life (Steenweg-de Graaff et al., 2012). In addition, folate also contributes to the synthesis of purine and pyrimidine (Duthie & Hawdon, 1998; Nimmo-Smith, 1954). Thus, altered folate levels could also affect DNA synthesis. Next to the epigenetic effects, impaired DNA synthesis could be involved in the effects of (possibly early-stress-induced) lack of these nutrients on brain function. In line with this, there is some evidence that maternal folate depletion affects DNA repair in adult mice offspring (Langie et al., 2013) and that early-adversity is associated with altered mitochondrial DNA copy number and telomere length (Picard et al., 2014; Tarry-Adkins & Ozanne, 2014; Tyrka et al., 2015).

Choline also belongs to the group of 1C metabolites (Zeisel et al., 2003). Choline, the precursor of the neurotransmitter acetylcholine, is of particular importance during perinatal life due to its pivotal role in cholinergic neurotransmission and phospholipid synthesis, having the ability to affect stem cell proliferation as well as apoptosis in the brain (Blusztajn & Mellott, 2012; Zeisel, 2004; Zeisel & Niculescu, 2006). Different from the other 1C metabolites that we discussed, choline can be synthesized to a limited extent by mammalian organisms, however, this is mostly insufficient and dietary intake of it is required (Zeisel & da Costa, 2009). Alterations in dietary choline levels affect the neuroendocrine system as well as emotional functions. For example, dietary choline supplementation during pregnancy and lactation mitigates the anxiety-related behaviors in rats (Schulz et al., 2014) and high choline in humans reduces CRH and cortisol levels in placenta and cord plasma, respectively (Jiang et al., 2012). Choline has also been reported to modulate DNA methylation (Mehedint et al., 2010). In fact, these effects of choline are at least partly due to epigenetic modifications, as DNA methylation of CRH and NR3C1 (nuclear receptor subfamily 3, group C, member 1; alias GR) promoters are increased in placental tissue.

The 1C metabolites mentioned in this section, i.e. choline, methionine and B vitamins, are metabolically interrelated in such a way that deficiency in one of these nutrients subsequently affects levels of other nutrients involved in the cycle and methylation. For example, vitamin B12 deficiency leads to hypomethylation due to accumulations of homocysteine and 5-MTHF, leading to the arrest of the methylation cycle and resulting in manifestations of folate deficiency due to a build-up of 5-MTHF. Interestingly, it appears that dietary choline is able to partially reverse the effects of folate deficiency during late gestation on neurogenesis and apoptosis in the fetal mouse brain (Craciunescu et al., 2010).

Finally, to add further to the complexity of these interactions, there is also evidence for a tight interaction between these methyl donors and fatty acids. Indeed, changes in folate status have been associated with alterations in lipid metabolism (Teng et al., 2011) and imbalances in maternal folic acid and vitamin B12 during gestation reduces offspring brain DHA levels (Rao et al., 2006; Roy et al., 2012).

To conclude, a lack of dietary methyl donors occurring in the window of critical development during EL may cause permanent effects through alterations in neurogenesis and the epigenetic machinery. Realizing the importance of these micronutrients, in particular during early development and considering the above-described effects of methyl donor and their deficiencies, raises the interesting possibility for nutritional interventions to modulate some of these effects. In fact, there is some evidence that supplementation with these metabolites can have lasting effects. For example, methyl donor supplementation diminishes adverse effects by decreasing global hypomethylation in the mice offspring of dams fed with a HF diet (Carlin et al., 2013). In addition, folic acid supplementation prevented hypomethylation on hepatic GR promoters in rat offspring of dams fed a PR diet during pregnancy (Lillicrop et al., 2005). On the cognitive level, methionine supplementation in rats is able to prevent the cognitive impairments caused by folate deficiency (Troen et al., 2008). Also, consequences of maternal behavior on DNA methylation in rats are reversible by infusing L-methionine (the precursor of SAM) in later life (Weaver, 2005). This preliminary evidence supports the possibility that supplementation with methyl donors may be effective to modulate lasting effects of EL adversities.

## Conclusions

In summary, EL adversity during critical developmental periods can program the developing brain and increase the vulnerability to develop psychopathologies in adulthood. We review intriguing evidence that ELS and EL nutrition lead to similar outcomes with respect to the resulting stress reactivity and emotional behavior. While it is out of the scope of our review, it is important to realize that many of the described effects of the various early environments might be part of a predictive adaptive response and may in fact prepare the organism to respond optimally under comparable situations encountered later in life, a concept known as the match-mismatch theory (Nederhof & Schmidt, 2012; Oomen et al., 2010, 2011). As ELS and nutrition are elements that interact and affect one another, it is difficult to distinguish the effects caused by each factor independently. One possibility is that nutrition, metabolic and stress hormones act synergistically in programming the stress system. To further explore this, we need to gain further knowledge as to how these factors affect one another, possibly involving epigenetic mechanisms. Elucidating the underlying mechanisms will not only advance our knowledge about the critical mediators, but also create the opportunity to further develop nutrition as a potential non-invasive intervention.

## Declaration of interest

The authors declare that the work was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest. For financial support, we would like to acknowledge NWO Meervoud, Food & Cognition and ISAO grants to AK and ISAO, Alzheimer Nederland and HersenStichting grants to PJJ.

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